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PREFACE

This 58th volume of *Advances* continues the sustained theme of definitive articles written by leaders in the field, providing comprehensive coverage of mature fields or selective treatment of evolving areas. In contrast to the strong emphasis on glycoconjugates and biological aspects in the preceding Volume 57, the contents of the present issue reflect mainly structural and synthetic aspects of simpler sugars.

Methodology for glycosidic coupling continues to pose challenges for the synthetic chemist, and the synthesis of defined oligosaccharide sequences remains a problem requiring great skill and experimental versatility. In contrast to the effective and widely available automated procedures based on solid-support technology for synthesis of oligopeptides and oligonucleotides, comparable procedures in the carbohydrate field have been lacking, on account of the complexities of linkage position, anomeric orientation, and protecting-group manipulation. Among the investigators addressing this problem, Seeberger (Cambridge, Massachusetts) and his coworkers Plante and Palmacci have made significant strides in developing the functional solid-phase automated synthesizer presented here. It provides practical feasibility for synthesis of selected oligosaccharide sequences, although further research to permit general application for other linkage patterns clearly remains necessary.

Although sugar derivatives containing unsaturated functionality were introduced back in Emil Fischer's time, and the rather inappropriate name "glycal" became a term that persists to this day, much of their chemistry remained confusing until the advent of NMR spectroscopy. Early surveys in Volumes 7 and 9 of this series, by Freudenberg and Blair respectively, were followed notably by Ferrier's landmark article in Volume 20, which demonstrated the exceptional versatility of unsaturated sugars in synthesis. Ferrier augmented his article soon afterwards, in Volume 24. The innovative leadership of Ferrier in this area of synthesis has become legendary, and here he and his colleague Hoberg (Lower Hutt, New Zealand) revisit the subject of unsaturated sugars in a definitive treatment from the current viewpoint.

A comprehensive survey of all classes of internal anhydrides of sugars is provided in this volume by Černý (Prague), encompassing cyclic sugars bridged by three-, four-, and five-membered oxygenated rings. Many such derivatives offer important potential in synthesis. Earlier articles in this series, especially those by Peat in Volume 2 and by Černý and Staněk in Volume 34, still provide useful background and older detail on these derivatives, as does the 1972 survey by Guthrie in Volume 1A of "The Carbohydrates, Chemistry and Biochemistry," edited by Pigman and Horton (Academic Press).

Two related chapters, contributed by de Lederkremer and Marino, and by Varela, both from Buenos Aires, deal with the processes and products of oxidation of carbohydrates, and offer extensive updating of the 1980 article by Green on acids and other oxidation products of sugars, and the one by Theander on oxidative and degradative reactions of sugars and polysaccharides, both published in Volume 1B of the Pigman–Horton treatise. These two articles from Argentina offer broad coverage of all aspects of carbohydrate oxidation, from both the fundamental view and from technological considerations. As an aid to the reader, titles of the cited articles are included in the extensive bibliographic references. Titles are also incorporated in the references cited in the Ferrier–Hoberg chapter. It is proposed to incorporate such titles on a standard basis in future volumes in this series.

The great biological significance of the sialic acids, nine-carbon 5-amino sugars, has long been recognized, and Schauer provided a definitive survey of their chemistry and biochemistry in Volume 40. Much more recently, the wide occurrence in microorganisms of related nonulosonic acids aminated also at position 7 has been demonstrated. Major work on these diamino sugars by three groups has led to the collaborative chapter by Knirel, Shashkov, and Tvetskov (Moscow), Jansson (Huddinge, Sweden), and Zähringer (Borstel, Germany) featured here as the last contribution to this volume.

The life and work of one of the greatest carbohydrate scientists of our time, Raymond U. Lemieux, is recalled here in a sensitive account by Bundle (Edmonton). During a remarkably productive career extending over more than half a century, Lemieux pioneered the application of NMR spectroscopy in chemistry, developed rational approaches for glycosidic coupling, made major contributions to our understanding of three-dimensional carbohydrate structures and protein binding, and made important contributions in the biomedical area. His own articles in these *Advances* include the chemistry of streptomycin in Volume 3, the mechanisms of replacement reactions in Volume 9, and in Volume 50 a consideration of Emil Fischer's "lock and key" concept of enzyme specificity.

With this present volume we welcome Peter H. Seeberger and Yuriy Knirel to the Board of Advisors.

Washington, DC
August 2003

DEREK HORTON

RAYMOND URGEL LEMIEUX

1920–2000

Raymond Urgel Lemieux, the seventh child of a pioneer homesteader, was born on June 16th 1920, in the small prairie community of Lac La Biche, two hundred kilometers northeast of Edmonton, Alberta. His mother died when he was only seven years of age and he was raised by his older sister, Alice. Raymond's father was an itinerant carpenter normally employed in the foothills of Alberta throughout the "dirty thirties" in the so-called coal branch. Consequently, he saw relatively little of his father, who nevertheless was dedicated to the welfare of his large family, a fact that left its mark with his son. The family moved from Lac La Biche to Edmonton, where in Lemieux's words "they lived in a basically Irish–French–Ukrainian ghetto, where the main challenge was to avoid associations that could lead to reform school." Although he did well in school, Lemieux had a passion for hockey and played in the Edmonton Junior Hockey League, but this experience, coupled with his slight physique, convinced him that he lacked the bulk to be truly successful in the sport. At this time his sister Annette met, and later married, a graduate student in physics, John Convey, who showed great interest in Raymond's high school studies and encouraged him to consider attending the University of Alberta. Supported in large part during his first year by tuition fees paid by his sister, Lemieux began his University education in the fall of 1939.

One of his major considerations in choosing to study chemistry was that the University employed a number of second year honours chemistry students as teaching assistants, an appointment he secured by virtue of leading his class in his freshman courses. This income (\$18 per month) was of crucial importance to his finances. In order to remain at University during this period, he had to volunteer for active duty, and throughout his undergraduate years he was heavily involved in the Officer's Training Corps. However, due to his involvement with research, he was never called up. At the suggestion of his favorite professor, Rubin Sandin, Lemieux worked with Jack Morrison on detonators. This work did not amount to much,

and in the Spring of 1943, after graduating, he stayed on with Morrison to investigate what happened to coconut charcoal when it was activated for use in gas masks.

Later that same year Lemieux left Edmonton for Montreal, a three-day train trip, and McGill University, where he registered for graduate studies with Clifford Purves, at the Pulp and Paper Research Institute of Canada. Research at McGill continued to be related to the war effort, first on oxycellulose and then on nitrocelluloses. Although he found the work to be not particularly engaging, the exposure to Purves and discussions with him kindled Lemieux's interest in stereochemistry, and cemented his decision to seek a career in research, primarily in the general area of carbohydrate chemistry. It was here in Purves' office, smoking hand-rolled cigarettes, that he became completely entranced by stereochemistry and fascinated by the structure and synthesis of sucrose, a topic to which he would later return, with considerable effect, on more than one occasion.

By 1946 he had completed his studies for his doctoral dissertation, and the possibility of postdoctoral studies attracted him. The discovery that the antibiotic streptomycin was a carbohydrate was of great interest, not least because ten years earlier his younger brother Gerard had died of a streptococcal infection. When he discovered that research on streptomycin was being pursued in the laboratory of Melville Wolfrom, Lemieux sought Purves' opinion as to whether he should apply for postdoctoral studies at Columbus, Ohio. The postdoctoral position he ultimately secured there was sponsored by Bristol Laboratories, an association that set the stage of a 25-year long research relationship between the young chemist and the pharmaceutical company. As important as this was, the move to Ohio held far greater significance, since it was at Ohio State University that Raymond Lemieux met Virginia McConaghie, who was studying for her Ph.D. degree in high-resolution infrared spectroscopy. They were married in New York City in 1948, and over the ensuing years they raised five daughters and one son, initially in Saskatoon, then Ottawa, and finally home to Edmonton. Referring to his family as one of his proudest accomplishments, he also acknowledged in his autobiography the dominant role of Jeanne (Mrs. Lemieux). Like many brilliant and driven scientists, his work made excessive demands on him and his family. Notwithstanding all these pressures he was proud to observe the considerable and diverse academic and professional achievements of all six children.

It was in the famous carbohydrate group at Ohio State University that Lemieux became involved in the structural elucidation of streptomycin. He also became fascinated by the configurational correlation of sugars and amino acids, and realized that he could address this unresolved question by

combining recent results from the Wolfrom group on the synthesis of peracetylated D-glucosamine diethyl dithioacetal with the Raney nickel desulfurizations he was then conducting. Reduction of the dithioacetal followed by periodate oxidation provided a route to L-alanine and hence its correlation to the relative configuration of D-glyceraldehyde. This work served as a milestone in stereochemistry by linking the stereochemical notation for these two important classes of molecules. Many years later Lemieux used D-glucose in a related fashion to synthesize one enantiomer of 1-deuterioethanol. This was one of the first examples of the use of a carbohydrate to provide a specific asymmetric center of known chirality in the synthesis of an unrelated molecule.

In 1947 Raymond Lemieux became Assistant Professor at the University of Saskatchewan, and two years later he joined the National Research Council's Prairie Regional Laboratory, also in Saskatchewan. During this period he attracted considerable public and scientific attention with the first rational synthesis of sucrose. In fact there was a brief dip in the commodities market for cane sugar when the news of his synthetic achievement broke and before the modest scale and yield of the reaction were properly appreciated. Two reactions involving oxidative cleavage of double bonds by sodium periodate and potassium permanganate, and periodate–osmium tetroxide were also published at this time and bear his name, the Lemieux–von Rudloff, and the Lemieux–Johnson reactions. During this, his first academic appointment, he began his studies and life-long interest in the chemistry of the anomeric center. Observations on neighboring-group participation, anomerizations, and preferential reactions of certain anomers set the stage for the synthesis of sucrose. The recognition accompanying this achievement led to an invitation to participate in the 5th Summer Seminar on the Chemistry of Natural Products at the University of New Brunswick in 1953. His lecture entitled “Reactions at the Anomeric Center of Acetylated Sugar Derivatives” in front of such luminaries of the period as R. B. Woodward, and D. H. R. Barton, gave Lemieux his first taste of contact with the leaders of the field, and also convinced him that he could hold his own in this company. It was obvious that the methods available at the time for determination of the stereochemistry at the anomeric center were certainly laborious and left a great deal of uncertainty. It was clear to him that there were special effects in play when it came to the conformational preference of certain pyranose derivatives, such that large substituents at C-1 of the pyranose ring did not occupy the expected equatorial position, but rather the axial orientation. In 1953, however, there was no way to obtain direct evidence for the preferred conformations of such molecules in solution. The solution to this problem lay just around the corner and coincided with his move to Ottawa in 1954.

The then president of the National Research Council, E. W. R. Steacie, had strongly urged the young Lemieux to consider a move to Ottawa to help recruit faculty to the Department of Chemistry at the University of Ottawa and develop an "atmosphere of research." Such were the hierarchical and paternalistic attitudes of the time, that one would have been ill advised to swim against such strong currents. Raymond Lemieux became Professor and Chairman of the Department of Chemistry at the University of Ottawa in 1954, and served as the Vice-Dean of the Faculty of Pure and Applied Science. During his tenure, he not only designed and supervised the building of a new chemistry department but, through his energy and perceptive staff appointments he established a flourishing research environment.

It was in Ottawa at the National Research Council that Lemieux first heard a presentation on NMR. He immediately began to speculate on the steric effects that might influence the chemical shifts of the protons of the pyranose ring. After approaching W. G. Schneider and H. J. Bernstein, Lemieux learned that if he provided manpower to assist in recording the spectra (a considerable task at that time) he would be able to study the NMR of the sugar acetates. With Rudolf Kullnig, a graduate student in Lemieux's group, and under the guidance of Harold Bernstein (NRC), the first NMR spectra of these compounds were obtained at 40 MHz. The work provided the long-sought definitive assessment of the preferred conformations of the sugar acetates in solution. Expansion of the approach led to the first application of ^1H NMR spectroscopy for the establishment of relative configurations of chiral centers in organic compounds, and thus the foundation of the Karplus relationship. It is interesting to note that this work was presented in the Karl Folkers Lectures at the University of Illinois in 1958, prior to publication. In attendance, and much impressed, was Martin Karplus, whose yet to be published theoretical work strongly aided in establishing this correlation as one of organic chemistry's most potent stereochemical probes. Karplus later wrote "Just as I finished the work on vicinal coupling constants, I heard a lecture by R. U. Lemieux on the conformations of acetylated sugars. I do not remember why I went to the talk because it was on organic chemistry. Lemieux reported results for vicinal coupling constants and noted that there appeared to be dihedral angle dependence, although the details of the behavior were not clear. However, it was evident that these experimental results confirmed the theory even before it was published." In the same year Lemieux discovered the anomeric effect, now recognized as a fundamental stereoelectronic phenomenon and one that governs the outcome of many organic reactions.

In 1961 Lemieux received an offer of a Professorship from the University of Alberta. Burdened with administrative duties and barely able to find time

for writing up his most successful work in Ottawa, this offer was too good to refuse. Discoveries of large conventional oil deposits had swelled the provincial coffers and the province was preparing to flex its newfound wealth through judicious investment in its main University. With carte blanche to build a strong Department of Chemistry, the recruitment of a young star was a cornerstone in the University's strategy. And so Lemieux returned to the University of Alberta Chemistry Department, where he maintained an active research program well into the 1990s. From 1966 to 1973, he was Chairman of the Division of Organic Chemistry and, aided by his influence and stature, the department grew to become one of the largest and foremost research centers for chemistry in North America.

His Alberta research group of the early 1960s undoubtedly represented one of the high points of his career. Several truly outstanding Ph.D. students during the period 1961–73 helped him establish an undisputed reputation as a world leader in his field. Key advances in the chemistry of orthoesters, glycals, and their nitrosyl chloride adducts, with Richard Morgan, Bert Fraser-Reid, and T. L. (Nag) Nagabushan, represented major breakthroughs during this period. Against this backdrop of new synthetic chemistry, and an increasing understanding of the anomeric effects, the exploitation of ^1H NMR spectroscopy to solve conformational and configurational questions was proceeding swiftly. The determination of the opposite relative signs of geminal and vicinal coupling constants in the proton magnetic resonance spectra of saturated organic molecules was made in 1961, followed in 1963 by the determination of the absolute configuration of dextrorotatory l-deuterioethanol, and in 1965 by the proposition of the reverse anomeric effect. Work on the NMR spectra of acetylated sugars continued, together with key developments in the use of NMR to determine the anomeric configurations of sugars and glycosides in D_2O solution. During the same period several postdoctoral fellows and students were engaged in the study of conformational equilibria in solution, using both NMR and chiroptical approaches. Such work added to the appreciation of the importance of the anomeric effect in dictating not only the anomeric preference of electronegative substituents but also the conformation of glycosides (exo-anomeric effect).

With the increasingly sophisticated understanding of reactions at the anomeric center, and the capability to contemplate synthetic targets that few others could consider in the late 1960s, attention turned to the selection of challenging targets. At this time circumstantial evidence was accumulating that complex oligosaccharides, whose structures were just then being solved, were critically involved in phenomena as diverse as cell–cell recognition and development, and control of glycoprotein biosynthesis and transport. It became apparent that the oligosaccharide chains of glycoproteins and

glycolipids could no longer be ignored, as these structures, in fact, carry messages essential for the control of many crucial cellular functions. The study of these new phenomena was critically hampered by the enormous difficulties encountered in trying to obtain even milligram quantities of structurally well-characterized carbohydrates. The most direct solution was to synthesize the required complex oligosaccharides, but this had not been attempted because of the difficulties involved.

At that time the synthesis of a disaccharide was considered a major undertaking, and preparation of the more elaborate oligosaccharides must have appeared as an unrealistic project. The successful completion of such a program required, at a minimum, the development of new glycosylation methods, especially for the synthesis of the α -glycosidic linkage, and the development of new methods for the structural analysis of both protected oligosaccharide intermediates and of the final synthetic products.

Largely as the result of research in his group during the 1960s, these essential methodologies for the stereospecific formation of the glycosidic linkage came to a climax in the early 1970s. For the first time, the synthesis of oligosaccharides of sufficient complexity that they would parallel the bioactivity of the naturally occurring structures could be accomplished. These new synthetic reactions included the oximino-chloride glycosylation method for the preparation of α -linked 2-amino-2-deoxyglycosides and the phthalimido glycosylation procedure for the preparation of β -linked 2-amino-2-deoxyglycosides. Most importantly, the development of the halide-ion glycosylation reaction permitted the synthesis of the hitherto elusive α -glycosidic linkage. These achievements resulted in four 1975 publications on the synthesis of the trisaccharide antigenic determinants for both the group B and Lewis-a human blood types, and opened the way for a host of other laboratories to join in the effort.

It is fair to say that Lemieux did not enjoy the process of manuscript preparation, and his breakthroughs in the rational synthesis of oligosaccharides appeared in several remarkable bursts of back-to-back publications. Thus the reaction of oximino chlorides and related papers appeared in the Canadian Journal of Chemistry as four consecutive publications in 1968, followed by eight consecutive publications in 1973. This extensive body of work would not have been achieved without the drive and commitment of Lemieux's close collaborator T. L. Nagabushan, who played a major role in helping Lemieux run his group during the period from the mid 1960s to 1973. An even more remarkable burst of publications followed in 1975 with the appearance of four papers in the Journal of the American Chemical Society announcing: the halide method, the first syntheses of the human blood group determinants, the use of a tether to

make artificial antigens, and production of blood group-specific polyclonal antisera.

In itself, the laboratory preparation of these antigenic determinants would have been a remarkable achievement. However, Lemieux's insight into the potential utility of these compounds was of such clarity that he foresaw their use as artificial antigens. His syntheses were conducted in such a way that the completed oligosaccharides incorporated a linking-arm to allow covalent attachment to appropriate carrier molecules. He also recognized that attachment to solid supports would provide biospecific adsorbents that would be of exceptional value in medical research. The immunization of test animals with these artificial antigens was shown to result in the production of antibodies specific for the carbohydrate determinants. These antibodies could then be isolated by affinity chromatography on the synthetic immunoadsorbent, thereby establishing a method for the preparation of carbohydrate-specific antibodies that was unrestricted by the scarcity and inaccessibility of the naturally occurring substances. This development allowed the production of antibodies specific for a large number of the human blood group determinants that were capable of detecting the corresponding naturally occurring structures on cell and tissue surfaces. The work established that immunization with a totally synthetic blood group oligosaccharide could result in the production of antibodies that were able to recognize this structure on the cell surface.

Several immediate impacts of this work followed. A major grant initiative to capitalize on the practical applications of these results was channelled to the Medical Research Council by the Natural Science and Engineering Research Council (NSERC), the traditional funding agency in Canada for research in chemistry. Although one of the top NSERC-funded investigators, Lemieux's research was especially manpower intensive and beyond the traditionally limited means of NSERC. This factor, coupled with the biomedical content of the research proposal, caused the proposal to be initially rejected. However, such was Lemieux's stature that a unique way was found to fund the research via the Medical Research Council of Canada, in what was almost certainly the first major funding by that agency for an essentially chemical research program. With this funding, the size of the group grew rapidly so that, while the initial foray in 1971 into blood group chemistry was spearheaded single-handedly by Hugues Driguez, the effort had gained momentum with the arrival of Don Baker and David Bundle in 1973. By early 1975 the MRC funding was in place, the group doubled in size, and in the fall of that year, Ole Hindsgaul, who was to become another of Lemieux's key collaborators, joined the group as a new graduate student. Implicit in the MRC funding was the intention to commercialize the potential of synthetic carbohydrate epitopes, and

ideas began to take root for the formation of what would now be called a biomedical start-up or spin-off company. The prescience of Lemieux's thinking was such that a company combining chemistry and immunology was years ahead of ventures that would later emerge in the much more progressive and adventurous climate of the USA. ChemBiomed, the new company, was formed in 1979. With the presence of many talented postdoctoral fellows and students in his group, significant quantities of blood group oligosaccharides became available. At about the same period high-field NMR was gaining momentum with the development of superconducting magnets that operated at field strengths above the previous limits of 220 MHz. The exploitation of NMR to answer stereochemical problems had already become a hallmark of Lemieux's publications, and with the advent of the pulsed, Fourier-transform technique, fast digital computers and cryomagnets, the capabilities of the technique again offered unique opportunities.

In 1975 Christian Pedersen and Klaus Bock (Technical University of Denmark), the latter a visiting scientist at the University of British Columbia with Professor Laurie Hall, paid a summer visit to Lemieux's laboratory. Bock immediately impressed Lemieux with his near-encyclopedic knowledge of NMR, especially as it applied to carbohydrates. It was also evident that work in Hall's lab was pointing the way forward in terms of being able to measure interproton distances by either T_1 measurements or NOE experiments. The stage was set and three years later Lemieux provided Bock with significant amounts of the blood group oligosaccharides. Thus began a collaboration that laid the foundations for a large body of pioneering studies on the determination of oligosaccharide conformation in solution, using NMR methods and semi-empirical calculations, termed the HSEA (Hard-Sphere-Exo-Anomeric) algorithm. Lemieux had anticipated some years earlier that the relative orientation of contiguous sugar residues in oligomeric structures was governed by the exo-anomeric effect. Confirmation of this idea was achieved through the observation of near-invariant vicinal coupling constants between the anomeric hydrogen and aglyconic carbon atoms in the nuclear magnetic resonance spectra of appropriately ^{13}C -enriched synthetic model glycosides. The development of the HSEA force field was basically an extension of this work. S. Koto had pioneered the development of the latter in Lemieux's laboratory during the period 1972–74, and with help initially from Louis Delbaere, and then Klaus Bock and Bernd Meyer, these calculations were converted into a computer program that was convenient to use and was made widely available during the 1980s. The initial NMR work on the blood group oligosaccharides was performed at 270 MHz on an instrument in Copenhagen, but in 1979 a new 400 MHz spectrometer was installed in the Department of Chemistry at the

University of Alberta. Shortly afterwards Klaus Bock spent a sabbatical leave in Alberta consolidating the conformational investigations on the blood group oligosaccharides. The initial work, largely completed by 1980, was written up and published in a long and challenging paper that appeared in the *Canadian Journal of Chemistry*. Two further papers appeared in 1982, the first justifying the importance of the exo-anomeric effect and the effectiveness of the new HSEA forcefield. The second paper dealt with the conformation of sucrose and unique experiments to detect an intramolecular hydrogen bond. This tremendous leap forward in the study of oligosaccharide conformation, as with many of Lemieux's other groundbreaking works, was first reported at a scientific meeting. So it was here that the papers dealing with both "The Lewis Antigens and Secretor Status," and "The Conformations of the Lewis Blood Group Determinants, Sucrose, and Kanamycin A," were reported in Japan, and appeared as published research lectures in the *Japanese Journal of Antibiotics* in 1979. Lemieux believed strongly that "the best part of a scientific career is to talk about what you have discovered when it is hot" which for him always preceded formal publication. So this work was no exception, but in this case publication as full papers did not have to wait as long as other earlier contributions, some of which only ever appeared as Abstracts of unpublished research lectures. Included under that heading are "Conformations and Relative Stabilities of Acetylated Sugars as Determined by NMR Spectroscopy and Anomerization Equilibria," and "Influence of the Anomeric Effect on the Reactivities and Conformations of Glycosides." Both were 1958 presentations to the American Chemical Society. The latter was the first public report concerning the exo-anomeric effect, and it was not until 1971 that a formal publication was presented on this topic in a paper entitled, "Effects of Unshared Pairs of Electrons and Their Solvation on Conformational Equilibria," *Pure Appl. Chem.*, **25**, 527–548 (1971).

Knowledge of the three-dimensional shapes of oligosaccharides was a prerequisite for appreciation of their biological activities, and the availability of these oligosaccharides in quantities sufficient for systematic study was an essential component in the successful research program that evolved during the next decade, 1975–1985. These developments allowed Lemieux to apply his discoveries to the human blood group-specific oligosaccharide determinants, including those with specificities designated serologically as A, B, O(H), X, Y, Lewis-a, Lewis-b, and related antigens. With knowledge of the three-dimensional shapes and flexibility of these important biologically active oligosaccharides, their binding to antibodies, lectins, and enzymes could, for the first time, be examined at the molecular level.

A strategy based on functional group replacement was developed to dissect the contribution of individual hydroxyl groups to the free energy

of binding. Synthesis of monodeoxy and methoxy derivatives as well as deoxyhalo derivatives allowed the discrimination of hydroxyl groups that could be hydrogen-bond donors and/or hydrogen-bond acceptors. Consideration was also given to topographical features whose existence could not be foreseen by simple consideration of the constituent monosaccharide residues. In order to elucidate the characteristics of the oligosaccharide binding which rendered possible their highly specific recognition by protein receptors, Lemieux initiated a vigorous synthetic program that produced over one hundred tri- and tetra-saccharide structures. These synthetic oligosaccharides were all analogues of the natural blood group determinants, which had been modified, either through removal of hydroxyl groups or by replacement of hydroxyls with other substituents. During this period two research associates played vital and leading roles in the molecular recognition studies. First, from late 1981 until 1986, Ole Hindsgaul helped lead Lemieux's group in studies on the lectins of *Ulex europaeus*, and *Griffonia simplicifolia* IV, and Lewis-b and blood group B monoclonal antibodies. Ulrike Spohr, who had joined Lemieux's group as a postdoctoral fellow in 1982, became his research associate from 1985 until he closed his research laboratory in 1995, and led in-depth studies of *Griffonia simplicifolia* IV and other lectins that recognized Lewis, or H-type antigens.

Through a systematic study of the binding of these analogues with their respective protein receptors, antibodies, and lectins, Lemieux was able to define the precise molecular features required for the specific recognition of complex carbohydrate determinants. An account of this work summarizes the development of his thinking during the period 1975–1996, "How water provides the impetus for molecular recognition in aqueous solution," *Acc. Chem. Res.*, **29**, 373–380 (1996), beginning with the "hydrated polar-group gate effect" as the key to the specificity in the recognition of complex carbohydrates, through to the idea of water reorganization as a major driving force for complexation.

The work culminated in the high-resolution crystal structure of the lectin of *Griffonia simplicifolia* complexed with the human Lewis-b tetrasaccharide, data that substantiated the crucial inferences that had been drawn from congener mapping of the binding site. Perhaps most dramatic was the confirmation, for this and several other systems, that only a very limited number of hydroxyl groups (often 2–3 out of some 10–12 present in an oligosaccharide epitope) are essential for acceptor recognition and biological activity. Furthermore, the bound conformation closely resembled a low-energy conformer observed in solution and predicted by HSEA calculation.

The results of Monte Carlo calculations on the hydration of oligosaccharide surfaces led Lemieux to conclude that the principal source of

binding energy between protein receptor and oligosaccharide epitope derived not from polar interactions between solutes, but from the collapse of perturbed water about the interacting, and polyamphiphilic surfaces. The return of these energetically disadvantaged water molecules from the closest hydration layers to bulk water would then provide a much larger source of free-energy change. These controversial ideas were refined over several years and arose from binding studies of some 100 synthetic tetrasaccharide congeners. It was gratifying that, at about the time he was winding down his group, strong supporting evidence for this interpretation appeared from calorimetry studies that showed 25–100% of the observed enthalpy of binding could arise from solvent reorganization.

Lemieux's profound influence on organic chemistry was due in large part to his enduring interest in the basic physical characteristics of molecules. Early appreciation of the implications of reaction mechanisms to carbohydrate chemistry [*Adv. Carbohydr. Chem.*, Vol. 9 (1954)] was clearly evidenced in the chemical synthesis of sucrose. The extensive research on the mechanism of substitution at the anomeric center, which lay behind this success, soon led to the recognition of the anomeric effect, followed later by the reverse-anomeric effect, and perhaps most important of all, the exo-anomeric effect. Theoretical support for these concepts followed many years after their recognition and acceptance as general, stereoelectronic effects in organic chemistry. This fundamental understanding of the chemistry of the anomeric center paved the way for new methods for synthesis of 1,2-*cis*-glycosides, a career-long interest. These major creative steps first generated methods for assignment of structural details, then provided tools for the assembly of complex structures, and finally placed him in a position to explore the subtleties of carbohydrate recognition phenomena.

Lemieux's leadership and commitment to the development in Canada of a viable, research-intensive industry have matched his scientific achievements. He founded three companies, R&L Molecular Research, Raylo Chemicals, and ChemBiomed Ltd., which sought to apply the creativity of university-based research to these objectives by capitalizing on the breakthroughs that occurred in his own research program on antibiotics and complex carbohydrates. Several practical applications have arisen from this work. Most significant amongst these is the development of immuno-absorbents to remove ABO iso-antibodies, and thereby permitting organ transplants across the ABO histocompatibility barrier. The current shortage of organs for transplant and the increasing attention being given to xeno-transplants suggests that this Lemieux technology, or its subsequent embodiments, may find expanded application. It should also be noted that much of the recent activity in the search for carbohydrate-based

therapeutics, such as sialyl Le^x anti-adhesion molecules, has its origin in his pioneering work.

Lemieux's academic and research accomplishments have been recognized in Canada, the United States, and Europe through numerous awards and honorary degrees. He received the American Chemical Society's Claude S. Hudson Award in 1966, was elected a Fellow of the Royal Society of London in 1967, and was awarded the Haworth Memorial Medal of the Chemical Society (London, UK) in 1978. He was the first recipient of the Izaak Walton Killam Memorial Prize (and of the Science and Engineering Research Council's Canada Gold Medal for Science and Engineering). Amongst other prestigious awards he received the University of Toronto Gairdner Foundation International Award (1985), the Royal Society of Chemistry Rhône-Poulenc Award (1989), the King Faisal International Prize in Science (1990), the "Albert Einstein" World Award of Science (1992) and, most recently, the Wolf Prize for Chemistry (1999).

Professor Lemieux made exceptional contributions to organic chemistry and especially the chemistry of carbohydrates. His work was a dominating factor in converting this field from an academic specialization to one of great practical importance in chemistry, biology, and medicine. He provided the area of carbohydrate chemistry—and its associated subjects—with extremely significant conceptual and experimental tools, and the fact that his influence on the subject has been so extensive, and has been exerted on so many occasions, shows a very rare and special degree of insight into chemical problems. His influential role was recognized when, with 21 world-renowned chemists, he was invited by the American Chemical Society to write his autobiography. The highly engaging series of books, "Profiles, Pathways and Dreams" documents the development of modern organic chemistry through the research careers of chemists who made seminal contributions to organic chemistry over a multidecade period of research. Lemieux's contribution, "Explorations with Sugars, How Sweet it Was," is an excellent account of his group's research from 1946–1990.

Much of Lemieux's science, certainly from the late sixties onwards, was an evolution of his intuition, especially with regard to his foray into molecular modelling and sugar–protein interactions. He had a great gift in this regard and did not spend hours studying and piecing together the extensive literature on immunochemistry, crystallography, and biophysical data of ligand–protein complexes. Nevertheless, his ideas drew heavily on his keen sense of the principles of physical organic chemistry and he always insisted on a huge body of thorough experimental work to support his theories.

Lemieux was fiercely Canadian and, in his own words, "pathologically Albertan." The vast majority of his publications appeared in the Canadian Journal of Chemistry, and he would often berate colleagues for not

supporting that journal, or for joining the American Chemical Society in preference to the Canadian Institute of Chemistry. Amongst his many awards, he was especially proud of his highest Canadian honors, the Canada Gold Medal for Science and Engineering, and the Order of Canada, to which he was appointed first as an Officer of the Order in 1968, and then in 1996 he was elevated to the highest level of recognition, a Companion of the Order of Canada. He was also especially honored by the decision of the Canadian Society for Chemistry to award a prize for Organic Chemistry bearing his name. In order to perpetuate and nurture the research he began, the University of Alberta established an endowed chair in his name, and to which he and Jeanne were major benefactors.

Shortly after his retirement Lemieux fought a major battle with prostate cancer. During his hospitalization and convalescence his group was most ably run by Ulrike Spohr. Although “formally retired,” he maintained his research group well into the 1990s, and despite an ongoing battle with failing eyesight caused by macular degeneration, he maintained his interest in carbohydrate–protein recognition. He continued to tussle with the topic of molecular recognition, and right up to his eightieth birthday in June 2000, he worked on his last manuscript despite constant struggle with the limitations imposed by his failing health.

In his early years Lemieux had a reputation as a demanding, tough supervisor and lecturer. He had intense drive, did not tolerate nonsense and always came to the point quickly, even at times brusquely. He was committed to excellence in himself and from those around him, and he did not hesitate to let his co-workers know if they were wrong about something. However, criticism was also given without rancour or harshness. Although his outward demeanour mellowed in the second half of his career, his drive was as intense as ever, as witnessed by his activity and the productivity of his group from 1975 to his official retirement, and beyond.

Notwithstanding his intense ambition and thrill for discovery, Lemieux was an unassuming individual who was devoid of pretensions. He was regarded by colleagues from around the world as good-humored and fun to be around, especially when he was relaxing in the bar or pub. His smile and infectious enjoyment of games are remembered by many. Indeed, many fortunate colleagues and visitors to the Department of Chemistry in Edmonton were delighted to be invited to spend time with him and his family at their cottage on Lake Edith, close to Jasper, in the heart of the Canadian Rockies. It was here in a sandpit at the side of the cottage, amongst the pine trees, that he reigned as undisputed champion of horseshoes, a favorite game, where he could combine his good humor and competitive nature with relaxation and the entertainment of visitors to his cottage. The “cottage” was one of his great loves and visitors through the

sixties and seventies did not escape free when they visited him there. This was no simple respite in the wilds, but a “work-in-progress” and the standing joke in his group was that if heavy jobs were pending, an invitation could mean cement mixing, under his close, demanding supervision and direction. Such were Lemieux’s diverse talents that he greatly enjoyed working with his hands and it was only in later years that he actually relinquished hands-on involvement in these projects to professional tradesmen.

On June 20th, 2000 Ray and Jeanne celebrated their birthdays in the company of their six children, seventeen grandchildren, relatives, friends, collaborators, and colleagues. Sadly, Ray died one month later.

To work in his group was both a delightful and daunting experience. He was rigorous and demanding in research and challenged one’s abilities in the most constructive and unobtrusive way, so that years after leaving his group one found oneself drawing on unrealized resources that could be traced back to his example and instruction. He was without doubt one of the outstanding chemists of the second half of the 20th century.

DAVID R. BUNDLE

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DEVELOPMENT OF AN AUTOMATED OLIGOSACCHARIDE SYNTHESIZER

BY OBADIAH J. PLANTE, EMMA R. PALMACCI, AND PETER H. SEEBERGER

Massachusetts Institute of Technology, Department of Chemistry,
Cambridge, MA 02139, USA

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I. INTRODUCTION

Practitioners of the rapidly growing field of glycobiology need access to isomerically pure oligosaccharides to understand fully the role of carbohydrates in biological processes. In order to meet the demand for molecular tools, new methods for the rapid production of carbohydrates are needed. Carbohydrates are the most stereochemically challenging class of biopolymers to prepare, and a variety of methods has been developed to address their synthesis. In addition to traditional solution-phase chemical synthesis, three methods have become increasingly popular for the construction of oligosaccharides. Enzymatic methods, orthogonal one-pot chemical methods, and automated solid-phase methods offer complementary approaches for the preparation of carbohydrates. Here we summarize our efforts to facilitate the procurement of oligosaccharides

and glycoconjugates through the development of automated solid-phase oligosaccharide synthesis.¹ It is anticipated that these and future developments in automated synthesis will allow the nonspecialist to procure significant amounts of defined oligosaccharides in a rapid fashion.

II. AUTOMATED SYNTHESIS OF BIOPOLYMERS

While no examples of automated solid-phase oligosaccharide synthesis had been reported until the work described here,² automated oligosaccharide synthesis was predated by efficient methods for the synthesis of peptides³ and nucleic acids.⁴ Here we briefly discuss the general features of each method, with particular emphasis on the scale and efficiency of peptide and nucleic acid synthesis.

Peptides of 20–40 amino acids in length are routinely prepared using automated protocols.⁵ Most commonly, solid-phase peptide synthesis is carried out from the *C*-terminus to the *N*-terminus. In this approach, an amino acid is bound to a support through the carboxyl end and the free amine is available for reaction.⁶ While polystyrene-based resins are commonly used, polyamide derivatives (namely PEGA) have seen increased use recently.⁷ Delivery of an *N*-protected amino acid with an activated carboxylic acid group leads to amide bond formation. Removal of the *N*-protecting group reveals another free amine for reiteration of the cycle. Both *tert*-butoxycarbonyl (Boc)- and 9-fluorenylmethoxycarbonyl (Fmoc)-protected amino acids are commonly used as building blocks for the preparation of milligram quantities of peptides. The high efficiency (98–99.9% per step) of solid-phase peptide synthesis has allowed for the synthesis of particular peptides on an industrial scale (kg/ton) in an automated fashion.

Similarly, deoxyribonucleic acid strands 100 bases in length are readily assembled using the phosphoramidite methodology.^{8,9} In this method, the first unit is attached to a controlled pore glass (CPG) support via the 3'-hydroxyl moiety. With the 5'-hydroxyl group of the support-bound nucleoside unprotected, a 5'-dimethoxytrityl-3'-phosphoramidite nucleotide is added and activated with 1*H*-tetrazole. Coupling to afford a dinucleotide product is followed by oxidation to secure the phosphodiester linkage. Subsequent removal of the dimethoxytrityl group with mild acid provides a convenient method of deprotection as well as analysis of the coupling efficiency via UV absorption.¹⁰ Remarkably, coupling efficiencies of 99.95–99.99% are commonly obtained on a 0.1–1.0 μmol scale.

A method capable of generating sequences 10–15 sugar units in length would be of interest with regard to carbohydrate synthesis. While coupling yields similar to those obtained in nucleic acid synthesis would be ideal,

initially a more realistic goal is to achieve 95–98% coupling efficiency. The automated method must also be able to generate significant quantities (0.1–1 mmol) of oligosaccharides. The need for relatively short sequences in significant quantities of material draw comparisons to peptide synthesis. Milligram to multigram quantities necessitate the use of high-loading polystyrene resins, as in solid-phase peptide synthesis. Other supports, such as CPG, are better suited for smaller-scale synthesis owing to their low loading (60–100 $\mu\text{mol/g}$).

III. CARBOHYDRATE SYNTHESIS

The structural diversity of glycans has been appreciated for many years. On one hand, the extraordinary diversity of carbohydrate sequences found in nature is responsible for their intricate biological properties. Conversely, this variance makes the analysis and study of oligosaccharides a slow and challenging process.¹¹ Carbohydrates are unlike the other major classes of biopolymers as they are often characterized by highly branched motifs. Each monosaccharide unit has multiple possible sites for attachment to the next sugar moiety. Additionally, each glycosidic linkage connecting two sugar units can adopt one of two possible isomeric forms. There are thus over one thousand different trisaccharides possible when the nine monosaccharides commonly encountered in mammalian carbohydrates are combined. This richness in sequence variation complicates the synthesis of carbohydrates, and distinguishes them from other classes of natural products. Due to the structural complexity of most glycan sequences, several methods have been developed for the synthesis of such carbohydrates, using enzymatic, solution-phase, and solid-phase techniques.

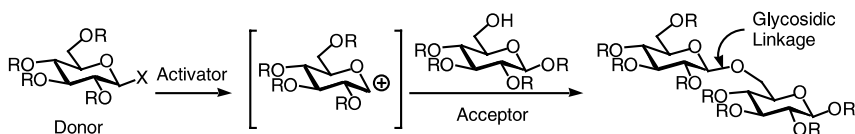
1. Enzymatic Methods

Alternatives to the traditional synthetic methods for the procurement of carbohydrates make use of enzymatic methods. Enzymatic techniques rely on the high specificity prevalent in glycosyltransferase-mediated glycosylations.¹² Utilizing nucleotide sugar diphosphates (NDPs) as building blocks, glycosyltransferases assemble complex carbohydrates in aqueous media. A major advantage of this method is the ability to prepare sophisticated structures without the need for protecting-group manipulations on either the building blocks or the desired product. While certain carbohydrates can be prepared using a particular transferase, the narrow scope of transferase-mediated glycosylations necessitates the isolation and purification of multiple enzymes to synthesize diverse structures. Additionally, the high cost associated with nucleotide sugar diphosphates makes this method

unattractive for large-scale synthesis. Potential solutions to the challenges in enzymatic oligosaccharide synthesis include the regeneration of NDPs¹³ *in situ* via immobilized enzymes.¹⁴ Considerable research in this area is currently ongoing and should lead to new, more efficient, and flexible enzymatic methods.

2. Solution-Phase Chemical Synthesis

The glycosylation reaction is one of the most thoroughly studied transformations in organic chemistry.^{15,16} In the most general sense, a glycosylation is the formation of an acetal connecting two sugar units (Scheme 1). The majority of glycosylating agents follow similar paths of reactivity.¹⁷ The anomeric substituent acts as a leaving group, thereby generating an electrophilic intermediate (Scheme 1). Reaction of this species with a nucleophile, typically a hydroxyl group, leads to the formation of a glycosidic linkage. This reaction may proceed via a number of intermediates, depending on the nature of the leaving group, the activating reagent, and the solvent employed.



SCHEME 1. General mechanism for chemical glycosylations.

Glycosyl trichloroacetimidates,¹⁸ thioglycosides,¹⁹ glycosyl sulfoxides,²⁰ glycosyl halides,^{21,22} glycosyl phosphites,²³ 4-pentenyl glycosides,²⁴ and 1,2-anhydro sugars²⁵ are among the most reliable glycosyl donors (Fig. 1). Despite the wealth of glycosylating agents available, no single method has been distinguished as a universal donor. In contrast to peptide and oligonucleotide synthesis, the inherent differences in monosaccharide structures make it unlikely that a common donor will prevail. Rather, individual donors will see use in the construction of certain classes of glycosidic linkages.

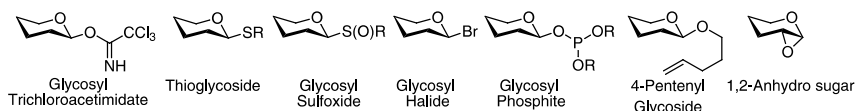


FIG. 1. Commonly used glycosylating agents.

3. Orthogonal One-Pot Methods

The desire to streamline the synthesis of carbohydrates and allow non-experts to prepare carbohydrates on demand has led to the design and evaluation of efficient one-pot methods. A solution-phase orthogonal method that relies on thioglycosides as glycosyl donors is the OptiMer™ strategy of Wong.²⁶ Analysis of the reactivity profiles for over a hundred different thioglycosides using a computer program allows for prediction of the optimal set of donors required to generate a given polysaccharide. This method involves the one-pot sequential addition of donors with decreasing reactivity.²⁷ The reactions are performed manually in solution, with the oligosaccharide chain grown from the nonreducing to the reducing end. Factors affecting the relative reactivity value (RRV) for a thioglycoside include the type of sugar used and the nature of the protecting groups employed.

This approach is useful for the synthesis of short, functionally dense oligosaccharide sequences, as exemplified by the synthesis of the globo H hexasaccharide.² Currently, efforts are underway to develop a set of building blocks from which the majority of carbohydrate sequences can be prepared. A challenge inherent to this method is evident when structures containing more than one identical linkage are desired. The need for orthogonal reactivity and sequential addition of donors necessitate the use of more than one building block (with different RRVs) for the same linkage, thereby adding to the overall number of building blocks needed. Although there are still limitations to the OptiMer™ method, it represents the first example of a computer-assisted program for oligosaccharide synthesis.

Another notable example of orthogonal one-pot glycosylations using thioglycosides is that of Takahashi and co-workers.²⁸ A library of 54 linear trisaccharides was prepared in parallel on a Quest 210 synthesizer, using the strategy already outlined. Similarly, 18 branched trisaccharides were also prepared in excellent overall yield (64–99%). This highly efficient procedure and the successful use of a manual synthesizer should lead to more instrumentation advances. Restrictions as to the overall length of the oligosaccharides prepared by one-pot methods currently hinder their widespread use.

4. Solid-Phase Chemical Synthesis

Solution-phase oligosaccharide synthesis remains a slow process due to the need for iterative coupling and deprotection steps, with purification at each step along the way. To alleviate the need for repetitive purification events, solid-phase techniques have been developed.^{29,30} In solid-phase

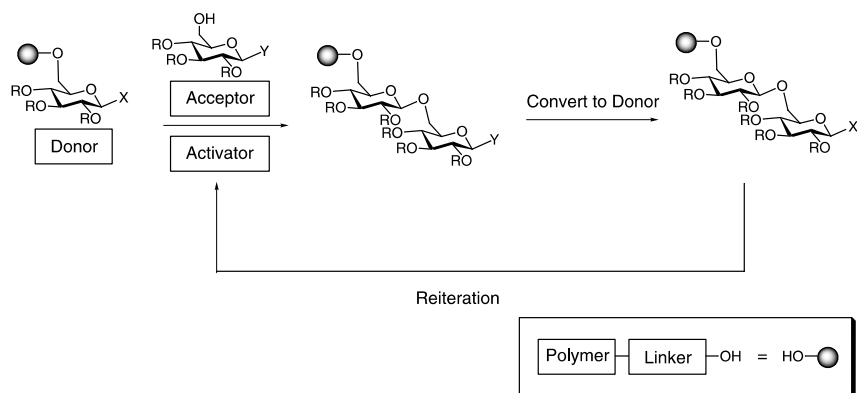


FIG. 2. Donor-bound solid-phase carbohydrate synthesis.

oligosaccharide synthesis there are two methods available (Figs. 2 and 3). The donor-bound method links the first sugar to the polymer through the nonreducing end of the monomer unit (Fig. 2). The polymer-bound sugar is then converted into a glycosyl donor and treated with an excess of acceptor and activator. Productive couplings lead to formation of polymer-bound disaccharide, while decomposition products remain bound to the resin. Elongation of the oligosaccharide chain is accomplished by converting the newly added sugar unit into a glycosyl donor and reiteration of the above cycle. Since most donor species are highly reactive, there is a greater chance of forming polymer-bound side products using the donor-bound method.

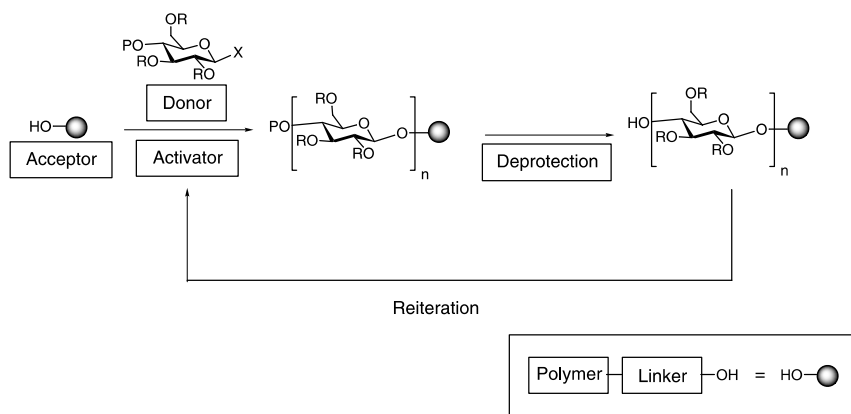


FIG. 3. Acceptor-bound solid-phase carbohydrate synthesis.

Alternatively, acceptor-bound strategies have found considerable use in solid-phase oligosaccharide synthesis (Fig. 3). In this approach, the first sugar is attached to the polymer at the reducing end. Removal of a unique protecting group on the sugar affords a polymer-bound acceptor. The reactive glycosylating agent is delivered in solution and productive coupling leads to polymer-bound oligosaccharides, while unwanted side products caused by donor decomposition are washed away. Removal of a unique protecting group on the polymer-bound oligosaccharide reveals another hydroxyl group for elongation.

While the merits of the donor-bound method have been demonstrated by Danishefsky and co-workers,³¹ the most popular and generally applicable method of synthesizing oligosaccharides on a polymer support remains the acceptor-bound strategy. The ability to use excess glycosylating agents in solution to drive reactions to completion has led to widespread use of this method. All of the aforementioned glycosylating agents have been utilized with the acceptor-bound method to varying degrees of success.³⁰

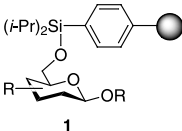
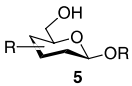
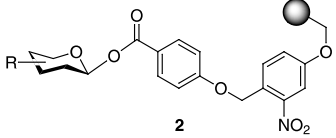
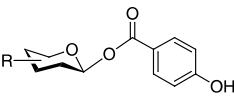
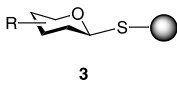
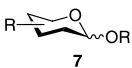
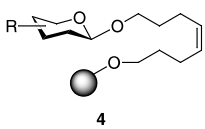
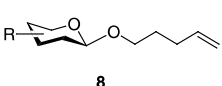
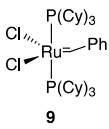
5. Solid-Phase Linkers

A critical element of any solid-phase synthesis strategy is the choice of an appropriate linker group connecting the first sugar to the solid support (Table I).³² The linker must be inert to the glycosylation conditions as well as the deprotection conditions. Equally important is the need for a high-yielding cleavage event at the conclusion of a synthesis. Several acid- and base-labile linkers, similar to those employed in peptide and oligonucleotide synthesis, have been modified for oligosaccharide synthesis.³²

Silyl ethers are most commonly used for monomer attachment to a polymer support under the donor-bound paradigm. Linkers such as diisopropyl phenylsilyl ether (**1**) are stable to mildly acidic and strongly basic reaction conditions, and have proven valuable when glycosyl trichloroacetimidates, glycals, glycosyl fluorides, and glycosyl sulfoxides are employed.³³ Liberation from the polymer support is accomplished upon treatment with fluoride sources, affording the free oligosaccharide unprotected at the original point of attachment. Due to the frequent use of silyl ethers as temporary protecting groups in oligosaccharide synthesis, the incorporation of a silyl linker often leads to significant challenges when differentiating the remaining hydroxyl groups.

A class of photolabile linkers has been developed to circumvent the use of silyl ethers as linkers and allow for the use of temporary silyl protecting groups.^{34,35} Photolabile linkers, such as **2**, often involve the use of *o*-nitrobenzyl ether groups. This functional group is stable to a variety of conditions; however, cleavage from the polymer support is often slow and

TABLE I
Linkers and Cleavage Methods for Solid-Phase Oligosaccharide Synthesis

Linker	Cleavage Product	Cleavage Conditions
 <p>1</p>	 <p>5</p>	Fluoride ion
 <p>2</p>	 <p>6</p>	UV-radiation
 <p>3</p>	 <p>7</p>	NBS, ROH or Hg ⁺⁺
 <p>4</p>	 <p>8</p>	 <p>9</p>

yields vary. Nonetheless, photolabile linkers offer another degree of orthogonality that is valuable when designing a synthesis.

A linker strategy that is unique to oligosaccharide synthesis involves the attachment of the first sugar to a polymer support via a thioglycoside. As already discussed, thioglycosides are moderately stable to acid and are inert under basic conditions. Thioglycosides, such as **3**, are cleaved from the polymer support upon addition of such thiophilic reagents as *N*-bromosuccinimide or Hg(O₂CCF₃)₂ in the presence of an alcohol or water, to afford either acetal or hemiacetal products, respectively.^{36,44} The obvious limitations of this linker are the incompatibility with thioglycoside donors and the limited stability to treatment with acidic activators. Also, a mixture of anomers is possible and control of the anomeric ratio is difficult, since the cleavage event occurs at the reducing end.

More recently, linkers similar to **4**, making use of alkene metathesis as the cleavage method, have been developed.^{37,38} Alkene-type linkers are stable to acidic and basic reaction conditions, and the double bond acts as a handle for the final cleavage event. This is an attractive option because the linker

functionality is inert under commonly used coupling and deprotection conditions, and the final cleavage step is compatible with numerous protecting groups. Importantly, the cleavage product contains an alkene group, thereby allowing for additional functional group manipulations.

As with solution-phase oligosaccharide synthesis, no single glycosylation method or linker strategy has distinguished itself among the variety of solid-phase techniques available. The abundance of linker strategies provides useful flexibility when planning a synthesis. It is anticipated that the development of novel linker and cleavage strategies will allow for the synthesis of increasingly complex carbohydrates using solid-phase methods.

IV. DESIGN OF AN AUTOMATED SOLID-PHASE OLIGOSACCHARIDE SYNTHESIS STRATEGY

At first glance, the automated synthesis of carbohydrates appears to be a formidable challenge. The multitude of branched sequences and variety of monosaccharide units necessitate the execution of long linear synthetic strategies. The inherent difference in reactivity and stereoselectivity of glycosylating agents also adds to the complexity of carbohydrate synthesis. Taking these factors into consideration, our laboratory systematically developed a strategy to address the viability of automated solid-phase oligosaccharide synthesis.

Our approach to oligosaccharide synthesis relied on the acceptor-bound solid-phase method. This method formally reduces the synthesis of carbohydrates to a repetitive cycle of glycosylation and deprotection events. It was reasoned that the repetitive nature of an acceptor-bound glycosylation method rendered it ideal for automation. Therefore, we set out to investigate the potential variables in such a scheme.

The acceptor-bound method necessitates the appropriate choice of polymer support and linker functionality. We chose to investigate the use of swelling and nonswelling polystyrene-based resins, as well as polyethylene glycol (PEG)-grafted polystyrene. These resins were selected for their moderate to high-loading capacity (0.2–1.0 mmol/g) and stability to acidic and basic reaction media. Our prior solid-support efforts using polystyrene-based Merrifield's resin (1% cross-linked) were promising; however, we were interested in exploring the properties of other resins.^{37,39} Another support that proved useful for carbohydrate synthesis was the highly cross-linked, polystyrene-based Argopore® resin.⁴⁰ In contrast to conventional polystyrene supports, Argopore® is a nonswelling resin that is compatible with aqueous and organic solvents. Attempts to functionalize polyethylene glycol grafted polystyrene supports, such as Tentagel®, with our linker were unsuccessful.⁴¹

An octenediol linker was selected as a convenient method of attachment to the polymer support.³⁷ Furthermore, the desired oligosaccharide could be readily obtained via cleavage by alkene metathesis to afford 4-pentenyl glycosides. 4-Pentenyl glycosides are versatile intermediates that can be used as glycosyl donors, coupled using free-radical chemistry to thiols, or oxidized to serve as linkers in glycoconjugate synthesis.⁴² Additionally, octenediol-functionalized resins were proven to be stable to a number of routine transformations in carbohydrate chemistry.³⁷

Another important aspect of our acceptor-bound strategy was the delivery of donors in solution. In selecting donors we considered their stability, reactivity, ease of synthesis, and activation under homogeneous reaction conditions. The use of insoluble reagents (such as powdered molecular sieves) would not be compatible with an automated instrument.

The most frequently used building blocks for solution-phase oligosaccharide synthesis include anomeric trichloroacetimidates and thioglycosides. Although thioglycosides are generally shelf-stable compounds that display excellent glycosylation properties, they often demand the use of *N*-iodosuccinimide (NIS) as an activator. The partial solubility of NIS in organic solvents, as well as the requirement for powdered molecular sieves in the reaction vessel, led us to forego the use of thioglycosides in our automated method. Glycosyl trichloroacetimidates, on the other hand, are routinely activated with trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) under homogeneous reaction conditions. Furthermore, trichloroacetimidate donors are reliable and efficient species that are activated in a catalytic manner.

We were interested in designing a synthesis whereby a variety of readily prepared donors could be utilized. The need for flexibility arises from the broad reactivity spectrum of glycosylating agents. Divergence in activity is common when comparing glycosyl donors of different monosaccharides with different protecting-group patterns. Previous efforts employing glycosyl phosphate donors were promising both in solution and on a solid support.^{37,43} Glycosyl phosphates are activated under homogenous conditions and are a class of highly reactive compounds. In addition to their favorable glycosylation properties, glycosyl phosphates are conveniently prepared from commercial starting materials. A one-pot procedure for the synthesis of glycosyl phosphates from glycal precursors can be readily applied to the construction of glucosyl and galactosyl phosphates in multigram quantities.⁴³

Another critical consideration was the development of an effective protecting-group strategy. We chose to employ benzyl ethers as “permanent” protecting groups, not to be removed during the course of intermittent deprotection events, because of their stability under moderately acidic and

strongly basic reaction media. Esters were selected as temporary protecting groups due to their ease of removal. Both acetyl and levulinoyl esters were chosen, based on prior work with their removal from support-bound oligosaccharides.⁴⁴ The removal of levulinoyl esters (N_2H_4 , pyridine–acetic acid) was readily accomplished in the presence of acetyl-, benzyl-, and pivaloyl-protected hydroxyl groups. Additionally, acetates were removed via saponification with sodium methoxide in methanol–dichloromethane. A solvent system with adequate swelling properties for polystyrene resins was required during each glycosylation, deprotection, and washing step. While swelling is less essential when macroreticular polymers are used, any reaction employing lightly cross-linked polystyrene-based resins would suffer poor yields when conducted under inappropriate reaction conditions.

In order to automate the synthetic process, we reconfigured a commercially available peptide synthesizer. An Applied Biosystems (ABI) Model 433A synthesizer was chosen because it was amenable to modification and capable of carrying out batchwise syntheses on a millimole scale (0.1–1.0 mmol) (Fig. 4). Reagent bottles equipped with the chemicals necessary for oligosaccharide synthesis, and containers with washing solvents, were installed on the instrument. While many of the manipulations in peptide chemistry are carried out at ambient temperature, most glycosylation events are performed at low temperatures.¹⁵ To address this need, we designed a double-walled reaction vessel (8 mL internal volume) with inlet and outlet hose fittings (Fig. 4). The temperature ($-50\text{ }^{\circ}\text{C} \rightarrow 40\text{ }^{\circ}\text{C}$) of the reaction vessel was controlled by connection to a Julabo® circulating bath. The vertical positioning of the reaction vessel in

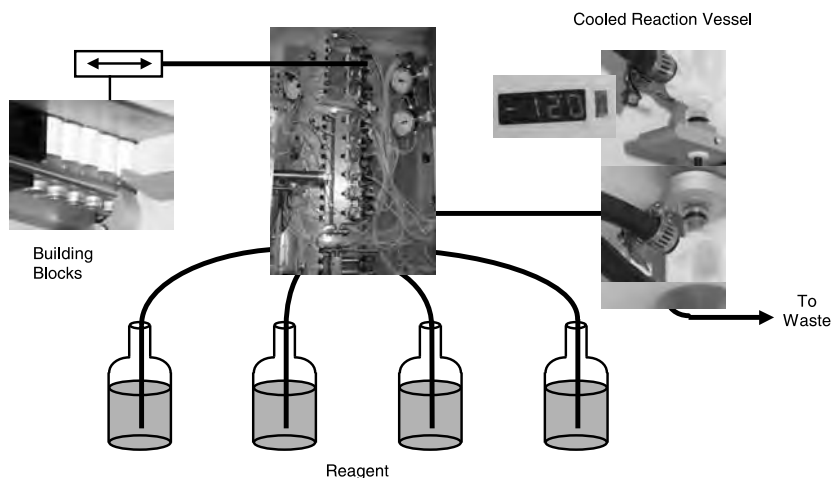


FIG. 4. Schematic design of an automated solid-phase oligosaccharide synthesizer.

the instrument demanded that a glass frit be installed on the bottom of the apparatus. With this design, we were able to load and remove resin from the top of the reaction vessel.

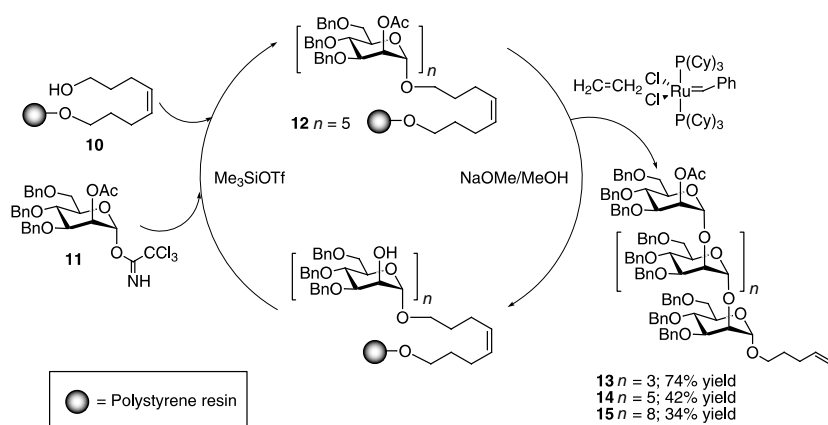
1. Automated Synthesis of Poly α -(1 \rightarrow 2)-D-Mannosides

With a synthetic strategy and an instrument in place, we explored the automated synthesis of poly α -(1 \rightarrow 2) mannosides. Initially, we developed a coupling cycle to control the quantity of reagents delivered, as well as the length of each step (Table II). Glycosyl trichloroacetimidate **11** was employed and activated with catalytic Me₃SiOTf (Scheme 2). Removal of the C-2 acetyl group was accomplished with sodium methoxide in methanol–dichloromethane. The sequence of events outlined in Table II was utilized with octenediol-functionalized 1% cross-linked polystyrene in the synthesis of pentamannoside **13** (Scheme 2). Under these conditions, **13** was prepared in only 14 h, or approximately 3 h per monomer unit added. The nonswelling highly cross-linked Argopore® resin was also successfully employed in this cycle with similar results.

TABLE II
Cycle Used with Glycosyl Trichloroacetimidate Activation and Acetate Deprotection

Step	Function	Reagent	Time (min)
1	Couple	10 Eq. donor and 0.5 eq. Me ₃ SiOTf	30
2	Wash	Dichloromethane	6
3	Couple	10 Eq. donor and 0.5 eq. Me ₃ SiOTf	30
4	Wash	Dichloromethane	6
5	Wash	1:9 Methanol–dichloromethane	6
6	Deprotection	2 \times 10 Eq. NaOMe (1:9 methanol–dichloromethane)	80
7	Wash	1:9 Methanol–dichloromethane	4
8	Wash	0.2 M Acetic acid in tetrahydrofuran	4
9	Wash	Tetrahydrofuran	6
10	Wash	Dichloromethane	6

We evaluated the purity of the final resin-bound pentasaccharide using on-bead analytical methods.¹ Characterization of the resin-bound pentamer **12** was performed using high-resolution magic angle-spinning nuclear magnetic resonance (HR-MAS NMR).^{45,46} The two-dimensional NMR spectra revealed characteristic anomeric resonances between 97 and 103 ppm. In addition to the HMQC results, homonuclear total correlation spectroscopy (TOCSY) HR-MAS analysis distinguished the five anomeric resonances. In a direct comparison, resin-bound **12** and an authentic sample



SCHEME 2. Synthesis of poly α -(1 \rightarrow 2) mannosides using glycosyl trichloroacetimidates.

of **13** showed excellent correlation, with minor line broadening of the resin-bound sample.⁴⁷

The facile synthesis of **13** in high yield and purity prompted us to undertake the synthesis of larger poly α -(1 \rightarrow 2) mannosides. Applying the coupling cycle described in Table II, heptamer **14** and decamer **15** were synthesized, with stepwise yields of 90–95%. Heptamannoside **14** was prepared in 20 h and in 42% overall yield while we manually synthesized **14** on the solid support in 14 days and in only 9% overall yield.³⁷ A striking feature of the automated solid-phase method was the efficiency with which reactions took place. Based on these results, it is evident that repetitive reactions carried out on an instrument can be accomplished rapidly and with high yields.

A useful feature of this synthesis was the ability to recover excess donor. In using the auxiliary waste feature as a donor-recovery function, we were able to isolate a significant portion (50–60%) of unreacted donor **14**. Hydrolyzed donor and 1 \leftrightarrow 1'-linked disaccharides were among the other products recovered. The solvents used in the synthesizer were commercial HPLC grade CH_2Cl_2 and tetrahydrofuran (THF), and were not dried prior to use. The use of a drying agent in the reagent and solvent bottles on the synthesizer may lead to suppressed hydrolysis of the donor and further increased yields.

2. Automated Synthesis of β -Glucans Using Glycosyl Phosphates

Given our success with the use of trichloroacetimidate donors, we sought to explore the use of glycosyl phosphates in an automated protocol.¹

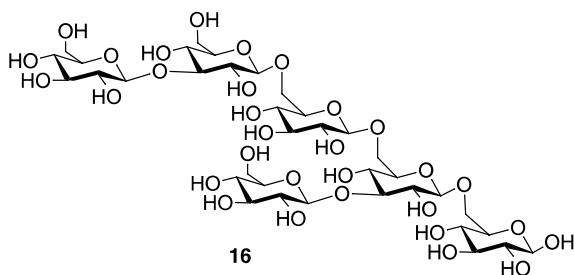


FIG. 5. A representative β -glucan oligosaccharide.

The phytoalexin elicitor (PE) family of β -D-glucans (Fig. 5) was selected as a target because these oligosaccharides had been synthesized previously in solution^{48,49} and on the solid support.^{50,51} It was our intention to investigate not only the application of glycosyl phosphates to automated solid-phase synthesis, but also to compare our method to the previously described reports of PE syntheses.

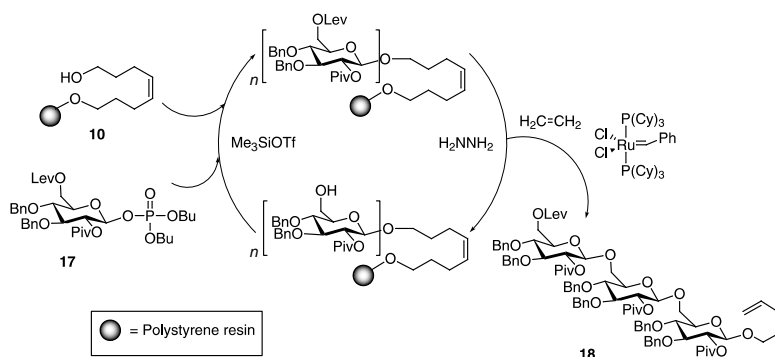
Our retrosynthesis of the branched β -(1 \rightarrow 3)/ β -(1 \rightarrow 6) PE structures suggested glycosyl phosphate donors **17** and **19** as potential building blocks. The levulinoyl ester was chosen as a temporary protecting group for O-6 because it could be easily removed, and yet under acidic conditions was less prone to migration than other esters.⁵² To ensure complete β -selectivity in the glycosylation reaction, the 2-*O*-pivaloyl group was installed. Glycosyl phosphates **17** and **19** were prepared from the corresponding glycals (92 and 84% respectively).

With gram quantities of **17** and **19** in hand, the coupling and deprotection conditions were adjusted for the use of glycosyl phosphates and levulinoyl esters (Table III). Glycosyl phosphate **17** was reacted at -15°C for 15 min (Scheme 3). As anticipated from previous studies,⁵³ deprotection of the levulinate ester was accomplished at $+15^\circ\text{C}$ (15 min) when 3:2 pyridine–AcOH was used as the solvent system.* Introduction of an additional washing cycle following deprotection of the levulinoyl group ensured removal of any excess hydrazine. As with previous solid-phase examples, double glycosylations and double deprotections were employed to guarantee high stepwise yields. Incorporation of these modifications to the automated cycle resulted in the formation of β -(1 \rightarrow 6) trisaccharide **18** (Scheme 3) in excellent yield (92% by HPLC analysis).

*Other hydrazine solutions using mixed solvent systems (MeOH–EtOH–THF) were susceptible to precipitate formation and did not display adequate swelling properties.

TABLE III
Cycle Used with Glycosyl Phosphate Activation and Levulinoyl Deprotection

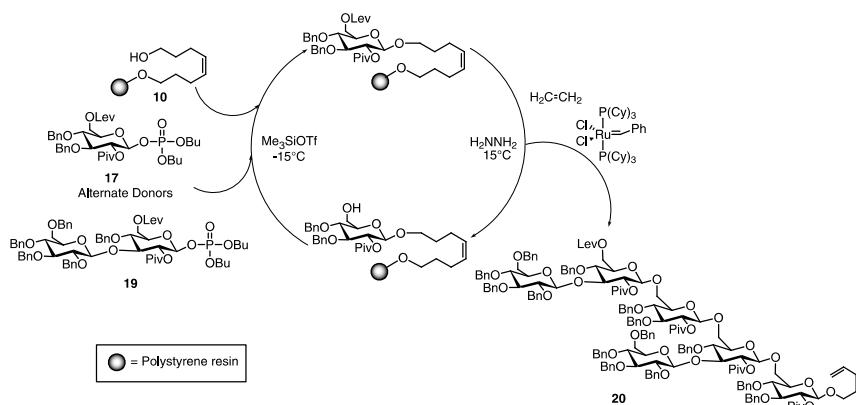
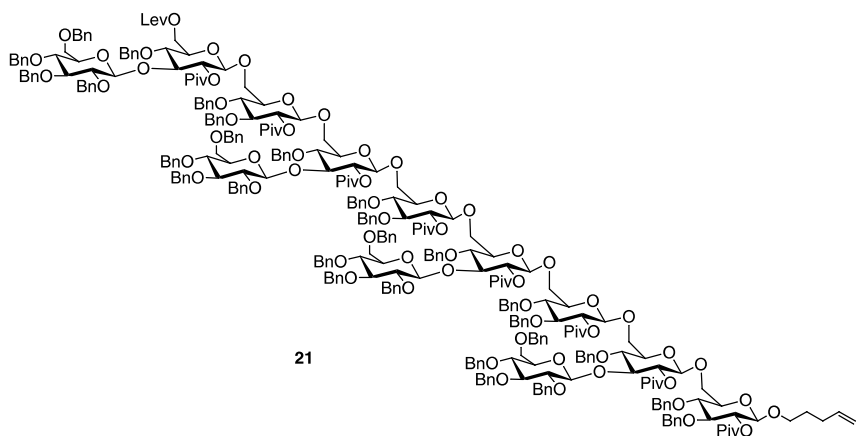
Step	Function	Reagent	Time (min)
1	Couple	5 Eq. donor and 5 eq. Me ₃ SiOTf	15
2	Wash	Dichloromethane	6
3	Couple	5 Eq. donor and 5 eq. Me ₃ SiOTf	15
4	Wash	1:9 Methanol–dichloromethane	4
5	Wash	Tetrahydrofuran	4
6	Wash	3:2 Pyridine–acetic acid	3
7	Deprotection	2 × 20 Eq. hydrazine (3:2 pyridine–acetic acid)	30
8	Wash	3:2 Pyridine–acetic acid	3
9	Wash	1:9 Methanol–dichloromethane	4
10	Wash	0.2 M Acetic acid in tetrahydrofuran	4
11	Wash	Tetrahydrofuran	4
12	Wash	Dichloromethane	6



SCHEME 3. Synthesis of β -(1 \rightarrow 6) triglucoside **18** using glycosyl phosphates.

Paramount to the success of this method was the execution of glycosylations at low temperature. As a comparison, we performed the synthesis of **18** at room temperature. Analysis of the HPLC data of the final cleaved products showed significantly fewer side products when glycosylations were performed at -15°C .¹

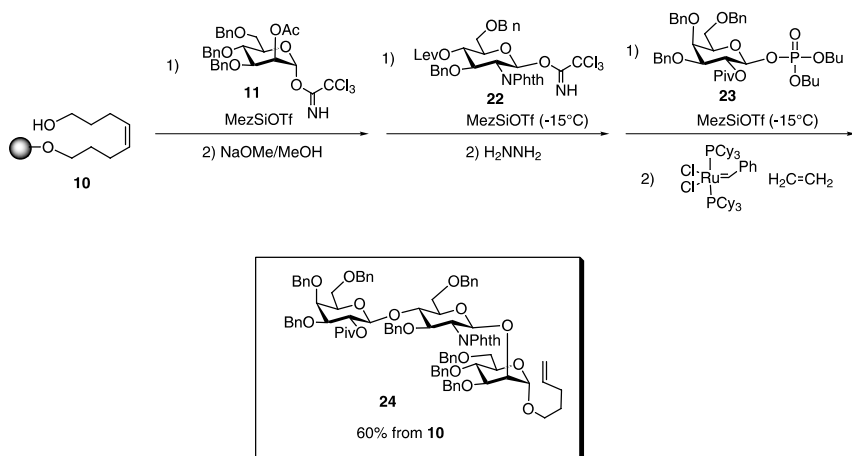
Using alternating phosphate building blocks, we prepared more complex PE oligosaccharides. Branched hexasaccharide **20** was constructed in high yield in only 10 h (Scheme 4). Finally, we prepared dodecasaccharide **21** (Fig. 6) in 17 h and $> 50\%$ yield using the same cycle. A similar dodecamer had been previously prepared manually on the solid support through the use of block couplings with trisaccharide thiodonors (10% overall yield).⁵⁰ Notably, our synthesis of **21** required the solution-phase synthesis of only two phosphate building blocks. The use of glycosyl phosphates in

SCHEME 4. Synthesis of hexasaccharide **20** using glycosyl phosphates.FIG. 6. Dodecamer **21** prepared with glycosyl phosphates.

the automated setting offers another degree of flexibility with regard to the donor options available. Furthermore, the successful deprotection of levulinoyl esters provides an alternative to acetyl esters as temporary protecting groups.

3. Complex-Type Trisaccharide

After developing procedures for the activation and coupling of anomeric trichloroacetimidate and glycosyl phosphate donors as well as for the deprotection of acetyl and levulinoyl esters, we designed a synthesis utilizing all aspects of our automated chemistry. Trisaccharide **24**, composed of three



SCHEME 5. Synthesis of trisaccharide using glycosyl trichloroacetimidates and glycosyl phosphates.

different monomer units, was chosen as a target structure and we devised a synthesis to incorporate different donors and temporary protecting groups (Scheme 5). Glycans containing this trisaccharide motif are difficult to prepare synthetically due to the presence of β -Gal-(1 \rightarrow 4)-GlcNAc and β -GlcNAc-(1 \rightarrow 2)-Man linkages.⁵⁴

Taking into consideration the activation and deprotection conditions necessary for the use of donors **11**, **22**, and **13**, we devised a suitable coupling cycle (Table IV). Employing the sequence outlined in Table IV, the synthesis of trisaccharide **24** was performed on a 1% cross-linked polystyrene support (Scheme 5). After the 10-h coupling cycle, trisaccharide **24** was cleaved from the support and analyzed by HPLC to afford **24** in 60% overall yield. We were encouraged by this result, as it was the first example incorporating all of the automated protocols into a single coupling cycle. Furthermore, the successful deprotection of a levulinate ester in the presence of a phthaloyl amine protecting group provided an orthogonal protecting-group strategy that can be generally applied to other sequences. It is anticipated that each degree of orthogonality developed for our automated protocol will enhance the speed and efficiency with which increasingly complex carbohydrates can be prepared.

V. SUMMARY AND FUTURE DIRECTIONS

We have developed an automated solid-phase approach for the chemical synthesis of oligosaccharides. Using an acceptor-bound solid-phase

TABLE IV
Cycle Used for the Synthesis of Trisaccharide 24

Step	Function	Reagent	Time (min)
1	Couple	4 Eq. donor 11 and 0.4 eq. Me ₃ SiOTf	30
2	Wash	Dichloromethane	6
3	Couple	4 Eq. donor 11 and 0.4 eq. Me ₃ SiOTf	30
4	Wash	Dichloromethane	6
5	Wash	1:9 Methanol–dichloromethane	4
6	Deprotection	2 × 10 Eq. NaOMe (1:9 methanol–dichloromethane)	80
7	Wash	1:9 Methanol–dichloromethane	4
8	Wash	0.2 M acetic acid in tetrahydrofuran	4
9	Wash	Tetrahydrofuran	4
10	Wash	Dichloromethane	6
11	Couple	4 Eq. donor 22 and 0.4 eq. Me ₃ SiOTf	30
12	Wash	Dichloromethane	6
13	Couple	4 Eq. donor 22 and 0.4 eq. Me ₃ SiOTf	30
14	Wash	Dichloromethane	6
15	Wash	1:9 Methanol–dichloromethane	4
16	Wash	Tetrahydrofuran	4
17	Wash	3:2 Pyridine–acetic acid	3
18	Deprotection	2 × 20 Eq. hydrazine (3:2 pyridine–acetic acid)	30
19	Wash	3:2 Pyridine–acetic acid	3
20	Wash	1:9 Methanol–dichloromethane	4
21	Wash	0.2 M acetic acid in tetrahydrofuran	4
22	Wash	Tetrahydrofuran	4
23	Wash	Dichloromethane	6
24	Couple	5 Eq. 23 donor and 5 eq. Me ₃ SiOTf	15
25	Wash	Dichloromethane	6
26	Couple	5 Eq. 23 donor and 5 eq. Me ₃ SiOTf	15
27	Wash	1:9 Methanol–dichloromethane	4
28	Wash	Tetrahydrofuran	4
29	Wash	Dichloromethane	6

glycosylation strategy in a specially designed instrument, poly α -(1 \rightarrow 2) mannosides as large as a decasaccharide were synthesized. The use of glycosyl phosphates was demonstrated with the synthesis of a dodecamer phytoalexin elicitor β -glucan. During this investigation, we relied on the use of HR-MAS NMR analysis as an on-resin analytical tool. The method described here is anticipated to have a significant impact on the field of oligosaccharide synthesis. Although there are still a number of challenges to be overcome, the automated construction of glycosidic linkages will allow for the preparation of a diverse set of carbohydrate for pharmaceutical and biochemical evaluation.

The advances in automation presented constitute an important first step toward alleviating the difficulty incumbent to carbohydrate synthesis.

Continued progress in the development of new methods for carbohydrate synthesis is anticipated to lead to further breakthroughs in automation. The construction of other linkages using a wide range of donors is on the horizon and will facilitate the synthetic process. Additionally, the definition of an orthogonal protecting-group ensemble applicable to a wide range of building blocks will lead to the production of diverse carbohydrate libraries.

While the path to enhancing automated synthesis is clear, a number of practical challenges remains. Given the recent success of synthetic methods, other bottlenecks have emerged. Notably, the purification of both fully protected and deprotected oligosaccharides is a laborious process. Improvements in currently available techniques are needed to allow for the expedient purification of synthetic material. More efficient methods for the analysis and sequencing of carbohydrates are of major importance.

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SYNTHESIS AND REACTIONS OF UNSATURATED SUGARS

BY ROBERT J. FERRIER^a AND JOHN O. HOBERG^b

^aIndustrial Research Ltd., P.O. Box 31 310, Lower Hutt, New Zealand; and

^bSchool of Chemical and Physical Sciences, Victoria University of Wellington,
P.O. Box 600, Wellington, New Zealand

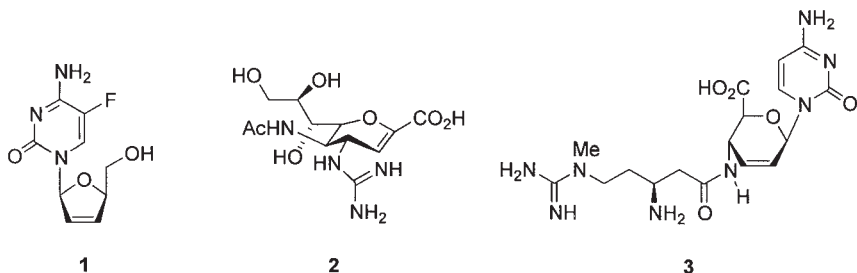
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I. INTRODUCTION

Sugar derivatives that contain double bonds have been developed and used so extensively that they almost certainly constitute the most versatile category of carbohydrate compounds available for use in synthesis. They may be applied both in the synthesis of complex members of the family and of a myriad enantiomerically pure noncarbohydrate compounds—notably, many of interest in medicinal chemistry. Furthermore, some unsaturated sugar derivatives have themselves been found to possess important therapeutic properties. For example, the unnatural L-nucleoside **1** inhibits reverse transcriptase and shows potent and selective anti-AIDS activity,¹ and the unsaturated neuraminic acid analogue **2** is the sialidase-inhibitory

anti-influenza drug Relenza which was developed by a team of university and industrial chemists using rational design.²

Only occasionally are compounds with unsaturated carbohydrate components found in Nature. A well-known example is blasticidin S (**3**) which inhibits blast disease of rice,³ and a most unusual case is that of a 2,6-dideoxy-trisaccharide “glycal” (1,2-unsaturated cyclic compound) isolated from a plant in India.⁴



This article surveys the chemistry of most of the important types of monosaccharide derivatives that contain single alkene groups—notably the glycals, which are extremely valuable starting materials for a vast range of synthetic transformations. A highly diversified group of compounds, which can vary in the position of, and in the substituents on the double bonds, are discussed; only occasional reference will be made to dienes, enones, alkynes, and compounds having unsaturation in the sugar substituents. Several reviews have covered the basic chemistry of carbohydrate compounds having unsaturation within their carbon skeletons.⁵⁻⁷ Recent developments have been appreciable.

II. GLYCALS

Compounds of this category are vinyl ethers having double bonds between C-1 and C-2 of pyranoid or furanoid aldose derivatives. Analogues with exocyclic C-1–C-2 double bonds in cyclic 2-ketoses are sometimes referred to as “*exo*-glycals” and are covered briefly in [Section IV.3](#); isomers with C-2–C-3 unsaturation in 2-ketoses can be considered as C-1-substituted glycals and are referred to in [Section II.3.a](#). Together the glycals and their derivatives constitute the most useful set of unsaturated carbohydrate derivatives for application in synthesis.

The anomalous “al” suffix used in the trivial names of members of the family in all probability originated at the very beginning of their history from aldehydic impurities present in the original preparations in Emil Fischer’s laboratory (see [Section II.2.d.i](#)). Compound **4**, the D-glucose

derivative "D-glucal," is the "parent" member, its formal name being 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, and the following trivial names are also in use: "D-allal," "D-gulal," and "D-galactal." These, like "D-glucal," are derived from the aldohexose epimers having the *R*-configuration at C-2. Consistent with this, the pentose-based name "D-xylal" is used, but not from any stereochemical reasoning, "D-arabinal" (D-arabinose having the *S*-configuration at C-2) is favored over "D-ribal." Commercially available tri-*O*-acetyl-D-glucal (**5**) is the best known and most useful member of the glycal set.

1. Preparation

a. Pyranoid Compounds.—Fischer and Zach's traditional method of preparation of glycals⁸ involved, for example, reduction of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (**7**) in aqueous acetic acid with zinc dust and catalytic Cu(II) salts, and was in use for many years; several adaptations have improved this procedure. For instance, a one-pot adaptation can be used to peracetylate the sugar, convert the product into the *O*-acetylated glycosyl bromide (for example, **7**) and bring about reductive elimination by use of a suspension of Zn and CuSO₄ in aqueous acetic acid. Almost quantitative yields of compound **5** are obtained by this method, but not all sugars convert with such high efficiency.⁹

Many attempts have been made to prepare glycal derivatives under aprotic, nonacidic conditions, but few of them have resulted in safe, efficient, and facile procedures. However, a straightforward and high-yielding method that can be applied on a large scale involves the addition of *O*-acetylated glycosyl bromides in ethyl acetate to suspensions of zinc dust in the same solvent to which 1-methylimidazole has been added. After a short time under reflux the mixture is filtered, and from the filtrate near-quantitative yields of the majority of the most common *O*-acetylated glycals are obtained.¹⁰ Use of catalytic amounts of vitamin B₁₂ [a source of Co(III)] together with zinc and ammonium chloride provides an additional efficient method.¹¹

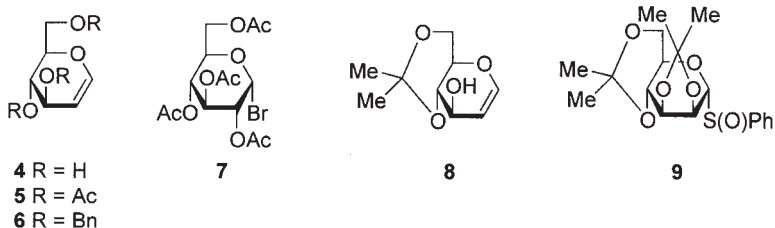
Alternatively, these products are obtainable with high efficiencies by addition of ester-, acetal-, or ether-protected glycosyl bromides or chlorides to tetrahydrofuran (THF) solutions of the titanium(III) dimer (Cp₂TiCl)₂, obtained from commercial Cp₂TiCl₂ and aluminum foil.¹² Otherwise, the halide can be treated *in situ* with the latter reagent in the presence of manganese metal.¹³ The original zinc-promoted reaction is believed to involve a two-electron transfer from the metal to the glycosyl halide-derived delocalized C-1 cation to produce a glycosyl carbanion from which the C-2 acyloxy group is lost. Conversely, the titanium complex-based method

appears to involve C-1 radicals and C-1-Ti-bonded intermediates that collapse with loss of $\text{Cp}_2\text{Ti(IV)ClOAc}$.

Similar chemistry involving glycosyl-Cr(III)-linked intermediates, produced from *O*-acetylated glycosyl bromides or chlorides by treatment with $[\text{Cr}(\text{OAc})_2 \cdot \text{H}_2\text{O}]_2$ in the presence of EDTA, also results in the formation of *O*-acetylated pyranoid glycals in high yields.¹⁴

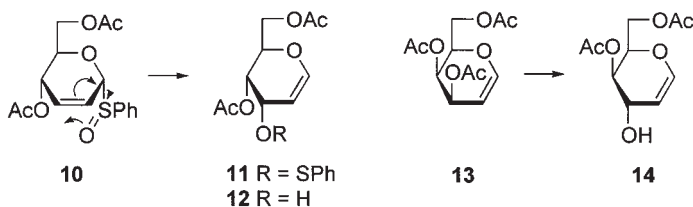
For glycosyl halides having alkyl or alkylidene substituents at O-2, potassium-graphite laminate (C_8K) in THF has been recommended over other reagents for the efficient conversion to glycals. Tri-*O*-benzyl-D-glucal (**6**) can be made by this means, and glycosyl halides having 2,3-acetal-*O*-protecting groups give glycal products with the hydroxyl group at C-3 specifically deprotected.¹⁵

Avoidance of ester *O*-protection in glycal precursors increases the range of leaving groups that can be used at the anomeric position, and particularly in these circumstances 1-thioglycosides, glycosyl sulfones, and glycosyl sulfoxides can be employed in glycal syntheses. An example of the last case is the formation in 86% yield of 4,6-*O*-isopropylidene-D-glucal (**8**) from 1-thio-D-mannoside sulfoxide (**9**) by treatment with butyllithium in THF at -78°C .¹⁶

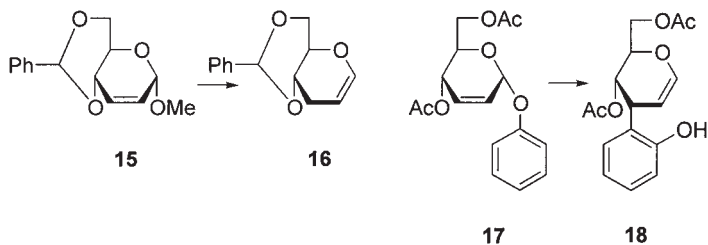


While elimination reactions offer the most general means of access to members of the glycal set, they are limited to cases for which suitable precursors are readily available. For the aldohexose-based compounds, this means that starting materials for the preparation of D-glucal and D-galactal (epimers at C-4) are readily available, but D-allose, D-altrose, D-gulose, and D-idose are relatively rare, and are therefore not good sources of D-allal and D-gulal, the C-3 epimers of the common D-glucal and D-galactal, respectively. An ingenious method is however available for effecting the required epimerizations from the latter compounds. Thus, tri-*O*-acetyl-D-glucal (**5**) is converted into *S*-phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio- α -D-*erythro*-hex-2-enopyranoside (see Section II.2.d.ii) which, on oxidation to the sulfoxide **10** followed by treatment with piperidine at room temperature, gives 3,6-di-*O*-acetyl-D-allal in 70% yield. Whether the [2,3]-sigmatropic rearrangement indicated in **10** occurs, followed by cleavage of the

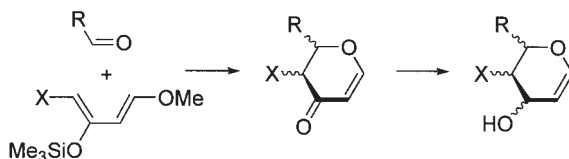
sulfenate **11** and acetyl migration from O-4 to O-3 of **12**, or whether the anomeric group of **10** is allylicly displaced with participation of the C-4 acetoxy group followed hydrolysis of the consequent 3,4-acetoxonium ion, is not known. However, this possible ambiguity is less apparent in the analogous reactions of tri-*O*-acetyl-D-galactal (**13**), which gives 4,6-di-*O*-acetyl-D-gulal (**14**) in 60% overall yield by this method.¹⁷



There are several examples of specific glycols being produced by the allylic rearrangement of 2,3-unsaturated compounds: the 3-deoxyglycol **16** is produced in 95% yield by treatment of the unsaturated glycoside **15** with lithium aluminum hydride,¹⁸ and thermal Claisen rearrangement of phenyl glycoside **17** affords the C-3-branched-chain glycol **18** in 55% yield. The β anomer of **17** reacts more readily to give a higher yield of the D-glucal-based C-3 epimer of compound **18**.¹⁹

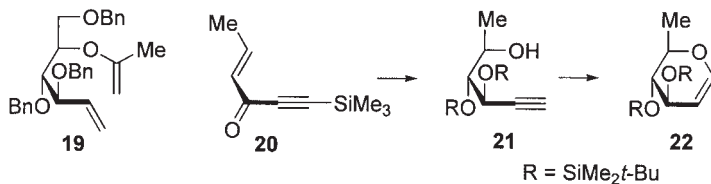


Limitations in the availability of naturally occurring sugars as suitable starting materials for the synthesis of glycols, and the protection-deprotection steps required when they are used, make alternative synthetic procedures attractive. The hetero-Diels-Alder reaction illustrated in [Scheme 1](#) represents such an alternative, and it has the advantage of being applicable under chiral conditions to the preparation of enantiomerically pure products.²⁰ An early example describes the condensation of benzyl-oxyacetaldehyde with 1-methoxy-3,4-di(trimethylsilyloxy)-1,3-butadiene in the presence of boron trifluoride etherate, followed by cleavage of the trimethylsilyl groups and β -elimination of methanol by use of trifluoroacetic acid. The product is the enone from which 6-*O*-benzyl-D,L-galactal is available on carbonyl reduction.²¹ Other methods, which, however, depend



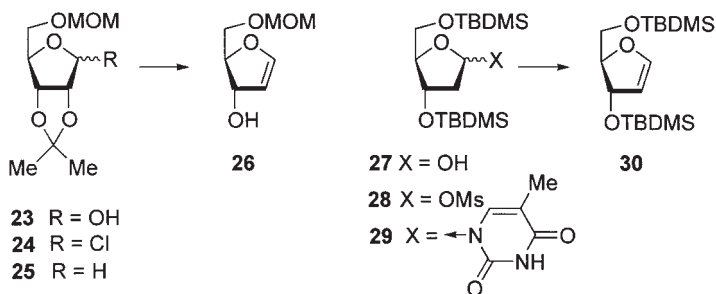
SCHEME 1

on rather complex syntheses of the required acyclic starting materials, have also been developed. For example, the diene **19**, made from 2,3,5-tri-*O*-benzyl-D-arabinose by methylenation at C-1, acetylation at O-4, and further methylenation of the ester carbonyl group, is ring closed by the Grubbs' olefin metathesis process to give tri-*O*-benzyl-1-*C*-methyl-D-glucal, the ring-closure step proceeding with 72% efficiency.²² A related type of approach starts from the noncarbohydrate enynone **20** which by enantioselective reduction of the carbonyl group and epoxidation, leads to alkyne **21** ($\text{R} = \text{tert-butyl dimethylsilyl}$, TBDMS). The cyclization of **21** to produce glycal **22** ($\text{R} = \text{TBDMS}$) is catalyzed by the products of photolysis of tungsten hexacarbonyl in the presence of a tertiary amine.²³



b. Furanoid Compounds.—Because of their relative planarity and the consequent ease with which elimination reactions to give furans may occur, furanoid glycols are much less robust than are their pyranoid analogues; particularly is this so for compounds with good leaving groups—such as esters—at C-3. In consequence, the zinc-based methods applied with *O*-acylated glycopyranosyl halides cannot be used to make furanoid glycal derivatives and little progress was made in preparing these compounds until 1980 when compound **26** (contaminated with a little of the reduced compound **25**) was prepared in 80% yield. The method involves conversion of the D-ribo-1,4-lactone-derived free sugar **23** to the glycosyl chloride **24** and subsequent treatment with lithium in liquid ammonia.²⁴ Since the use of this reagent limits the scale on which this reaction can be conducted, alternative methods applicable on multigram batches were developed—particularly for the subsequent production of nucleoside

analogues from the glycal products. Free sugar **27**, made from “2-deoxy-D-ribose” via the derived 1,4-lactone, affords the mesylate **28** which on heating in triethylamine gives the surprisingly stable glycal **30** in good yield.²⁵



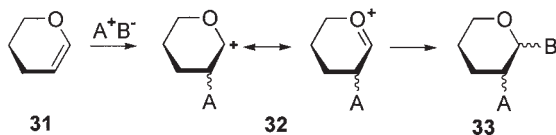
Otherwise, compound **30**, and differently *O*-substituted analogues, can be made efficiently from *O*-protected 2-deoxy nucleosides. Heating thymidine diether **29** in refluxing 1,1,1,3,3,3-hexamethyldisilazene in the presence of ammonium sulfate under an inert atmosphere gives **30** in 47% overall yield from the nucleoside. A notable feature of this approach is that thymidine itself can be converted directly to the unprotected parent of diether **30** with 80% efficiency.²⁶

Application of the potassium-graphite laminate method to, for example, 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranosyl chloride¹⁵ or the corresponding *S*-phenyl 1-thioglycoside,²⁷ and oxidation of phenyl 2-deoxy-1-selenofuranosides or the isomeric 2-phenylseleno-1,4-anhydroalditols with *tert*-butyl hydroperoxide and titanium tetraisopropoxide²⁸ represent other ways of making furanosyl glycols in good yields.

2. Reactions

Glycals and their derivatives undergo an extensive set of addition, substitution, and rearrangement reactions,⁵⁻⁷ many of which show good selectivities, and as a consequence are the starting materials for the synthesis of many types of compounds.

a. Addition Reactions.—(i) Polar Additions.—Numerous ionic additions to the double bonds of glycals can occur, with the most important affording access to 2-deoxy- and 2-amino-2-deoxy-glycosides and -oligosaccharides of appreciable significance in natural and bioactive products. Such additions commonly occur regiospecifically because of the directing effect of the ring oxygen atom within the enol ether function **31** which directs electrophiles



SCHEME 2

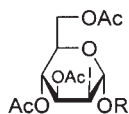
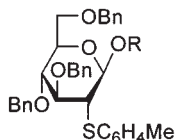
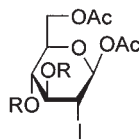
to the C-2 position, thus producing resonance-stabilized cationic intermediates **32**. Nucleophilic attack in consequence leads to the saturated products **33** (Scheme 2). When **A** is a hydrogen atom, it may be introduced directly as a proton or alternatively by way of reductively removable groups such as halogens on thioethers. Otherwise, **A** can be a nitrogen-incorporating group such as azide from which the amino function is derived by reduction. Glycosides result when the nucleophilic species is an alcohol or, as is often the case, a leaving group such as halogen that is subsequently displaced by an alcohol. Except when **A** is a hydrogen atom, such additions to glycals, even given the regioselectivity implied by **33**, can lead to four stereoisomers, and a required feature of all useful reactions is appreciable stereoselectivity in addition to regioselectivity.

In the synthesis of 2-deoxyaldoses and their derivatives, the stereochemical problem is decreased since C-2 is not a stereogenic center. However, specific methods are required for the preparation of their 1-*O*-substituted derivatives such as the often wanted β -linked glycosides.²⁹ Although many examples have been reported of the acid-catalyzed addition of water, alcohols, phenols, and carboxylic acids to glycal derivatives to give 2-deoxy-aldoses, -aldosides, and -aldosyl esters,⁵⁻⁷ the efficiencies of these processes may be affected by concurrent acid-catalyzed rearrangements (see Section II.2.d.i) and removal of *O*-protecting groups. As a consequence, procedures have been developed to preclude such side reactions. For example, treatment of *O*-acylated glycals with hydroxylic compounds in dry dichloromethane with catalytic amounts of triphenylphosphine hydrobromide,³⁰ or in acetonitrile containing lithium bromide (anhydrous unless for hydration reactions), with molecular sieves and dehydrated H⁺ from cationic resin (Dowex 50W-X8),³¹ result only in addition reactions at room temperature. Other mild methods of effecting net hydration of glycals include hydroxymercuration with mercury(II) acetate in aqueous tetrahydrofuran, followed by cleavage of the C-2-Hg bond by use of sodium borohydride,³² and treatment with *N*-iodosuccinimide in aqueous acetonitrile, followed by reductive removal of the C-2 iodo group from the first product.³³

When 2-deoxyaldoses are formed, their anomers are readily interconvertible. On the other hand, addition of alcohols or carboxylic acids in

acid conditions generate 2-deoxy glycosides or 2-deoxy glycosyl esters as mixtures of anomers with the α isomers normally predominating in the products derived from glucal and galactal or their derivatives. Whether the axial anomeric selectivity is ascribable to a “kinetic anomeric effect” favoring axial bonding to C-1 of protonated intermediates, or to “the anomeric effect” that thermodynamically favors axial products, depends upon whether those initially formed can anomerize. In the case of additions to D-allal derivatives, however, β products predominate^{34,35} because the axial C-3 substituents in the starting materials disfavor the formation of products that also have axial groups at C-1.

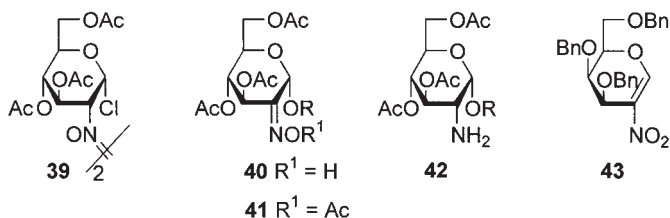
For the synthesis of specific 2-deoxy glycosides of the type commonly found in many natural products, methods that involve intermediates with reductively removable groups at C-2 are often used.^{35,36} For example, 2-deoxy-2-iodo- α -D-mannopyranosides (**34**) are available by reaction of tri-*O*-acetyl-D-glucal (**5**) with iodonium dicollidine perchlorate³⁷ or *N*-iodo-succinimide³⁸ in the presence of alcohols. On the other hand, the major products of reaction of tri-*O*-benzyl-D-glucal with alcohols in the presence of the sulfonium salt **38**, made from di(*p*-tolyl) disulfide, *p*-tolylsulfenyl chloride, and antimony pentachloride, are the β -D-*gluco* products **36**.³⁵ Modified procedures, which use the glycal-derived 2-substituted glycosyl donors **35**³⁹ and **37**,⁴⁰ have also been developed for the specific synthesis of 2-deoxy α - and β -glucosides, respectively. A further approach to the β -glycosides involves alcoholysis of 1,2-anhydro compounds (epoxides) produced by oxygenation of glycal derivatives (Section II.2.a.ii), followed by deoxygenation at C-2.⁴¹ More directly, appropriate glycosidase enzymes can be used to catalyze the addition of alcohols specifically to D-glucal and D-galactal to give 2-deoxy- β -glycosides, with D-galactal also being capable of adding unprotected sugar derivatives.⁴²

**34** R = alkyl**35** R = Ac**36****37** R = TBDMS

38 (*p*-TolS)₂S⁺*p*-TolSbCl₆⁻
(a sulfonium salt)

Additions to glycals can also give products from which glycosylating agents can be made for the specific synthesis of 2-amino-2-deoxyglycosides, and this approach adds to the methods available for making such glycosides

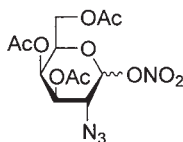
from the amino sugars themselves.⁴³ For example, treatment of tri-*O*-acetyl-D-glucal with nitrosyl chloride gives the dimeric nitroso adduct **39** which reacts with alcohols to produce 2-oximino- α -glycosides (**40**) by an HCl elimination-alcohol addition process. From these, 2-amino-2-deoxy- α -glucosides (**42**) are available after reduction with borane-THF and deacetylation of the *O*-acetyl derivatives **41**.⁴⁴ A much more recent approach uses Michael-like additions to 2-nitroglycals, such as **43**, made by addition of acetyl nitrate to *O*-benzylglycals, followed by base-catalyzed removal of acetic acid. Glycal **43** adds alcohols to give mainly 2-deoxy-2-nitro- α - or β -galactosides according to whether strong or mild bases are employed as the reaction catalysts, and these products can be reduced to the corresponding 2-amino-2-deoxyglycosides.⁴⁵



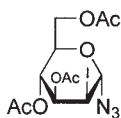
An alternative route to such compounds involves application of the azidonitration addition reaction using ceric ammonium nitrate and sodium azide first introduced with alkenes by Trahanovsky and Robbins.⁴⁶ The products from glycals are the 2-azido-2-deoxyglycosyl nitrates⁴⁷ which are convertible, for example, into corresponding 2-amino-2-deoxyglycosyl carboxylates, halides, xanthates, and trichloroacetimidates, all of which are good glycosylating agents.⁴³ From tri-*O*-acetyl-D-galactal the D-*galacto* adducts **44** are formed with high regio- and stereoselectivity and these open routes to 2-amino-2-deoxygalactosides.⁴⁷ On the other hand, the stereoselectivity is less with tri-*O*-acetyl-D-glucal, and 2-azido-2-deoxy adducts with the *gluco* or *manno* configuration are obtained depending on the temperatures and solvents used.⁴⁸

Addition of iodoazide results in 1,2-*trans*-related 2-deoxy-2-iodoglycosyl azides, which upon reaction with triphenylphosphine and alcohols in dichloromethane, lead to 2-deoxy-2-(triphenylphosphonioamino iodide) glycosides with inverted configurations at both C-1 and C-2, presumably via intermediate aziridines. In the case of tri-*O*-acetyl-D-glucal, the α -*manno* adduct **45** predominates (58%) over the β -*gluco* compound (35%) in the first step and leads to *N*-substituted glycosides **46** which give the peracetylated glucosaminides, such as **47** by treatment with sodium methoxide and reacetylation.⁴⁹ Similarly, tri-*O*-benzyl-D-glucal, with

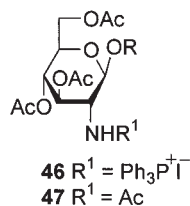
benzenesulfonamide and iodonium dicollidine perchlorate, gives in 78% yield the *N*-(2-deoxy-2-iodoglycosyl)benzenesulfonamide, which, by wet triethylamine-catalyzed rearrangement, affords the 2-(benzenesulfonyl)-amino-2-deoxy free sugar also in high yield.⁵⁰



44



45

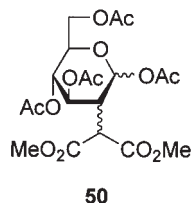
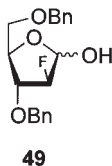
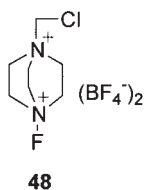


46 $R^1 = \text{Ph}_3\text{P}^+\text{I}^-$
 47 $R^1 = \text{Ac}$

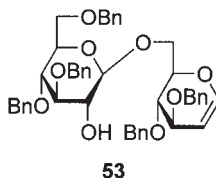
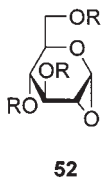
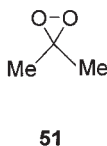
Other methods of introducing amino substituents at C-2 by glycal additions include the use of the (saltmen)Mn(N) complex and trifluoroacetic anhydride,⁵¹ and the photochemical addition of *N*-chloro-chloroacetamide.⁵² In both cases tri-*O*-acetyl-D-glucal gives 2-amino-2-deoxy-D-glucose adducts, in the former case with the hydroxyl group at C-1, and in the latter with chlorine which can be displaced by alkoxy at that position.

Hydrogen halides add to glycals to give further access to 2-deoxy glycosyl compounds and fluorine, chlorine, and bromine can all lead to 1,2-adducts that, as glycosylating agents, give access to 2-deoxy-2-haloglycosides.⁵⁻⁷ Of these, the fluorinated members are most important because of their use as inhibitors and mechanistic probes of glycosidases and glycosyl transferases. Practical difficulties associated with the synthesis of 2-deoxy-2-fluoro sugars and their glycosides are overcome by the use of Selectfluor (48), which, with glycals in the presence of water or alcohols, give these products. Tri-*O*-acetyl-D-glucal and -D-galactal afford mainly 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-mannose and -D-galactose, respectively, and the major free sugar derived from the relevant furanoid glycal is the D-*arabino* adduct 49.⁵³ This procedure has led to a powerful and direct route from glycal derivatives to 2-deoxy-2-fluoro-glycosides and -disaccharides.⁵⁴

Polar reactions are seldom used to add carbon-bonded groups to glycal double bonds, but hydroformylation with hydrogen and carbon monoxide in the presence of cobalt octacarbonyl as catalyst leads to 2-deoxy adducts with formyl groups attached to C-1.⁵⁵ The apparently anomalous inverse reaction by which *C*-malonyl groups bond to C-2 in the presence of manganese(III) acetate can be accounted for by the intermediacy of malonyl radicals. In this way, the reaction of tri-*O*-acetyl-D-glucal with dimethyl malonate in hot acetic acid affords mainly the glycosyl acetates 50 (66%, *gluco:manno*, 3.8:1).⁵⁶



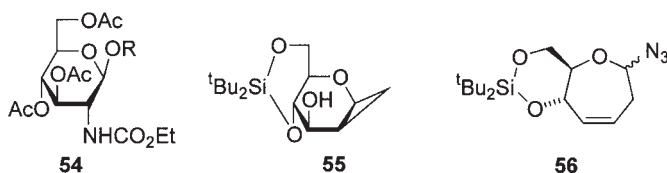
(ii) **Cycloadditions.**—Danishefsky introduced a new era of glycal chemistry when he showed that ether-protected glycals afford high yields of 1,2-anhydro adducts on treatment with dimethyldioxirane (**51**). Stereoselectivities of the reactions are very high with the products obtained having the epoxide ring *anti*- to the C-3 substituent. In the case of tri-*O*-benzyl-D-glucal, the selectivity is about 20:1, and when the size of the *O*-substituents is increased to *tert*-butyldimethylsilyl, no *manno* adduct accompanies the α -*gluco* epoxide **52** (R = TBDMS).⁵⁷ These epoxides are key moieties in Danishefsky's "glycal assembly" approach to the synthesis of oligosaccharides and glycoconjugates,⁵⁸ and they have been used to make specifically 2-*O*-unsubstituted β -glucosides and also the analogous β -thioglycosides and β -fluorides from which α -glucosyl linkages can be established. Reaction of benzylated epoxide **52** (R = Bn) with 3,4-di-*O*-benzyl-D-glucal under zinc chloride catalysis gives the disaccharide glycal **53** which, after benzylation of the liberated hydroxyl group, can be reprocessed to give the trisaccharide analogue. Since at any stage the glycal moieties can be converted, for example, to deoxy or amino sugars as already indicated (Section II.2.a.i), this approach affords an extremely versatile technology for the preparation of complex saccharides.



Photolysis of ethyl azidoformate causes loss of nitrogen and the formation of a nitrene that adds to the double bonds of glycals to give *N*-ethoxycarbonylaziridenes that react easily with alcohols to give products such as **54**,⁵⁹ but this approach does not appear to have become popular for making 2-amino-2-deoxy sugar glycosides.

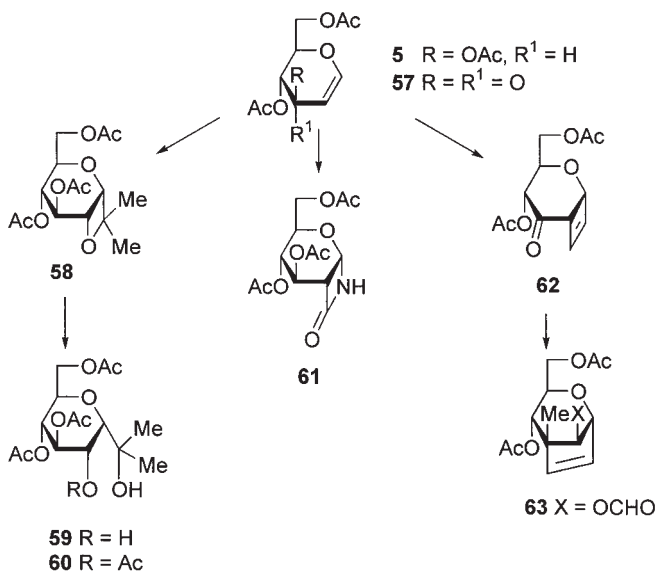
The cycloaddition of carbenes to glycals is an effective method for the formation of cyclopropanated carbohydrates with high stereoselectivity,⁶⁰

but different means of generating the carbenes lead to additions from the different sides of the double bonds. Thus it seems that carbenes derived by zinc mediation (as under Simmons–Smith conditions; Zn–Cu couple with diiodomethane) mostly give adducts formed on the side of the rings occupied by the C-3 substituents,^{61,62} while *anti*-addition occurs with carbenes derived from ethyl diazoacetate⁶³ or with dihalocarbenes.⁶² It is also evident, however, that the type of protecting groups present can influence the course of the reactions.^{60,64} With adduct **55**, which is produced with diethylzinc and diiodomethane,⁶¹ complexation of the zinc–carbene species with the allylic hydroxyl group may account, at least in part, for the *syn* selectivity. The products open routes to C-2 branched-chain compounds, but more particularly to specifically substituted oxepanes. For example, compound **55**, after *O*-acetylation, reacts at low temperatures with trimethylsilyl azide in the presence of trimethylsilyl triflate, to give compounds **56** with high efficiency as a 2:1 mixture of α , β anomers.⁶¹



Several examples are known of [2 + 2] cycloaddition reactions involving the double bond of glycal derivatives as illustrated in Scheme 3. Thus, tri-*O*-acetyl-D-glucal (**5**), when irradiated in acetone containing 1% 2-propanol with a high-pressure mercury lamp, gives adduct **58** together with the hydrolysis product **59** in high yield. Since the former is converted efficiently into **60**, a specific synthesis of 2-hydroxypropan-2-yl α -C-glucosides is available.⁶⁵ In related studies involving the addition of chlorosulfonyl and trichloroacetyl isocyanates to the double bonds of glycal derivatives, Chmielewski and colleagues have opened routes to β -lactam antibiotic compounds. Tri-*O*-acetyl-D-glucal (**5**) treated with the former reagent gives an adduct which, on reaction with lithium iodide to reductively remove the chlorosulfonyl group, affords compound **61** in 35% yield. This approach is unusual in having been applied successfully to furanoid glycal derivatives.⁶⁶

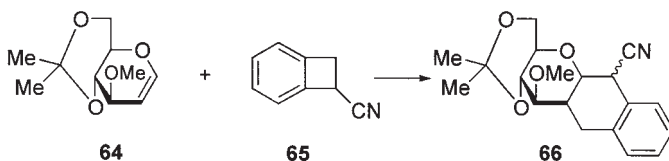
Reaction of the conjugated enone **57**, derivable directly from D-glucal (Section II.2.b), with acetylene in acetone at -20°C under a high-pressure lamp gives the cyclobutene derivative **62** (50%) convertible into the [3.2.1]bicyclic compound **63** which has the ring system of the B, C section of the antitumor mycotoxins of the trichothecenes. Rearrangement of **62** to **63** is effected by generating a tertiary alcohol center at C-3 and hence, with



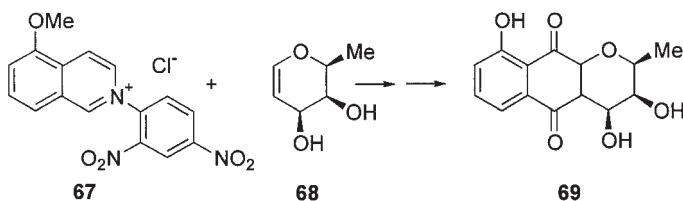
SCHEME 3

formic acid, a carbocation at this position.⁶⁷ Similar treatment of the 4,6-*O*-isopropylidene analogue of compound **57** results in the same addition reaction to give 81% yield of the cyclobutene.⁶⁸

Although most reported instances of [4+2] cycloaddition reactions involving the double bonds of glycals lead to the formation of heterocyclic six-membered rings, there are examples of cyclohexane ring-formation. Thus, D-glucal derivative **64**, heated with cyanobenzocyclobutane (**65**) at 170 °C, gives the adducts **66** in 65% yield by a Diels–Alder addition reaction involving a cyano-*o*-quinone methide intermediate (Scheme 4).⁶⁹ Further work from the Franck laboratory uses the Bradsher cycloaddition reaction to condense (CaCO₃ in MeOH, followed by aqueous acid) L-fucal (**68**) with the isoquinolinium salt **67** to give an intermediate tricyclic aldehyde which can be further transformed into (–)-cryptosporin (**69**, Scheme 5), the enantiomer of a fungal metabolite.⁷⁰

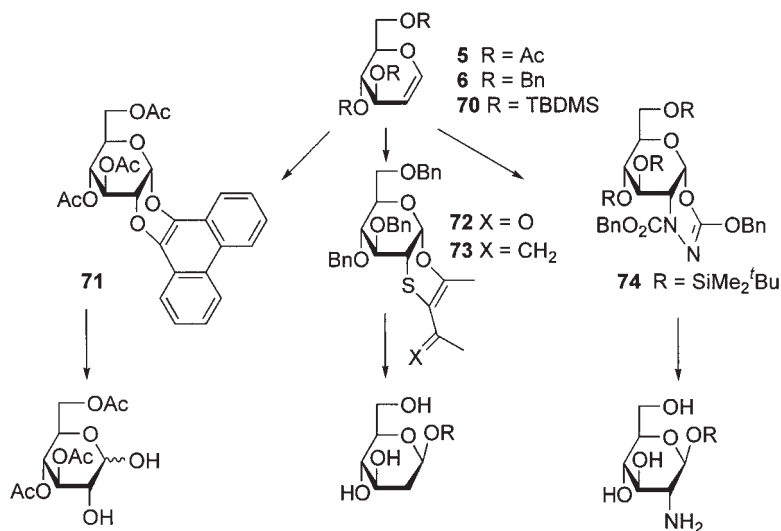


SCHEME 4



SCHEME 5

Several heterocyclic ring systems have been developed from the double bonds of glycals by cycloaddition processes, an early example being the UV-promoted addition of phenanthrenequinone to tri-*O*-acetyl-D-glucal (**5**) to give D-*gluco* adduct **71** in 50% yield. Ozonolysis of **71** gives 3,4,6-tri-*O*-acetyl-D-glucose, thus providing an overall method of stereoselectively hydroxylating the double bond of the glycal (Scheme 6).⁷¹ An analogous reaction involves the addition of 3-thionopentanedione (formed *in situ* from the analogous 3-phthalimidosulfonyl dione) to *O*-benzylated glycals to give adducts such as **72** [80% from tri-*O*-benzyl-D-glucal (**6**)]. These, following methylenation of the carbonyl groups, give dienes (**73** from **72**) that, with acid promoters, act as glycosyl donors to afford, in the case of **73**, β -glucoside derivatives that can be desulfurized at C-2. An additional route (compare Section II.2.a.i) to 2-deoxy- β -glucosides is therefore provided.⁷² It should be noted that this cycloaddition



SCHEME 6

reaction cannot be applied to *O*-acylated glycals, but it is applicable to nonacylated furanoid compounds, the stereochemistry favoring mainly *trans*-adducts when O-3 is substituted and *O*-3-*cis*-related products when it does not carry a substituent.⁷³

Dihydrooxadiazines can be made in related fashion and they too offer novel access to important products. For example, the *O*-silylated D-glucal **70**, irradiated at 350 nm in cyclohexane with dibenzyl azodicarboxylate, affords adduct **74** in 71% yield,⁷⁴ and this with an acid catalyst can be used as a glycosylating agent to make β -linked 2-amino-2-deoxy-D-glucosides.⁷⁵ This chemistry also is applicable to furanoid glycals.⁷⁴ Scheme 6 outlines the regio- and stereoselectivities of these cycloaddition reactions and their applications in synthetically useful processes.

b. Reactions at the Alcohol Functions.—The importance of glycal derivatives as starting materials for the synthesis of both complex carbohydrate and noncarbohydrate compounds points to the need for differentially *O*-substituted compounds, and a wide range of such compounds are available.

Selective acylation, sulfonylation, and silylation can be effected at the primary hydroxyl functions, 6-*O*-benzoyl, -tosyl, -trityl, and -*tert*-butyldiphenylsilyl-D-glucal, for example, being available by direct substitution.⁷⁶ Esters and ethers at O-3 are readily made by way of cyclic 4,6-*O*-substituted derivatives, such as 4,6-*O*-isopropylidene-D-glucal (**8**)⁷⁷ or, preferably, the 4,6-*O*-di-(*tert*-butyl)silane-diyl derivative **75**, which can be made in near-quantitative yield by use of di-(*tert*-butyl)silyl ditriflate in DMF at low temperatures.⁷⁸ As with other silyl ethers, this protecting group can be readily removed by use of fluoride ion, and it appears to have several advantages over the 4,6-*O*-tetraisopropylidisiloxane analogue that also has been used to make 3-*O*-substituted glycals.⁷⁹

Methods based on enzymic catalysis can be used to obtain 6-*O*-acyl esters of D-glucal and D-galactal, from which 3,6-diesters are obtainable in good yield by use of vinyl acetate, vinyl chloroacetate, or vinyl benzoate as the sources of the acyl groups.⁸⁰ Chemical silylations also follow this course, controlled *tert*-butyldimethylsilylation of the same glycals giving the 3,6-disilyl ethers in 90 and 83% yield, respectively, by way of the 6-ethers.⁸¹ As expected from these observations, the analogous 6-deoxy glycals, rhamnal and fucal, react selectively at the allylic O-3 sites,⁸² and while some results suggest that chemical acylations also show this selectivity, 6-*O*-*tert*-butyldimethylsilyl-D-glucal giving the 3-benzoate,⁸³ others make it clear that the positions of acylation can depend strongly on the conditions used. For example, while acetic anhydride in pyridine can give the 3- and 4-acetates of L-rhamnal in the ratio 1:3.5, benzoyl chloride in the same

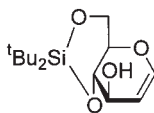
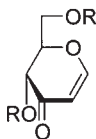
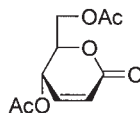
solvent affords the analogous benzoates, with the former predominating strongly (11.5:1).⁸⁴

A different approach to selective *O*-substitution involves preferential replacement of existing groups. When tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal is treated with phosphorus oxychloride–dimethylformamide complex in pyridine, the *O*-6 silyl ether is selectively and efficiently replaced by a formate ester (Vilsmeier–Haack reaction).⁸⁵

The reactivities of the hydroxyl groups of D-glucal and D-galactal are in the order $O-4 > O-3 > O-6$ for methylation and benzylation conducted in *N,N*-dimethylformamide via the sodium or lithium alkoxides or electrochemically.⁸⁶ These observations are corroborated by semiempirical calculations⁸⁷ and are in interesting contrast to the selectivities just given. A possible explanation is that while the last-reported data pertain to reactions of oxyions, the others may refer to those of the undissociated alcohols.

Oxidation of glycals occurs selectively at the allylic position and several reagents are available for the conversion of D-glucal into the enone **76**.⁸⁸ Reported yields are modest in most cases, but palladium acetate (1 equiv.) in DMF containing small proportions of water is highly effective, producing near-quantitative yields of the diacetate **77** after acetylation.⁸⁹ A procedure that uses catalytic proportions of palladium acetate in acetonitrile and ethylene is also very efficient.⁹⁰ However, the sensitivity of the enones is indicated by D-galactal being formed in a mixture with its expected 4-epimer.⁹⁰ Direct access to the acetylated enone **77** is afforded by reaction of the tri-*O*-protected D-glucal with [hydroxy(tosyloxy)iodo]benzene [PhI(OH)OTs] in dry acetonitrile under nitrogen at 0 °C, these conditions permitting analogous direct oxidation of tri-*O*-acetyl-D-galactal and -D-allal and of *O*-benzylated glycals.⁸⁸ On the other hand, *O*-silylated glycals can be converted into the 1-en-3-uloses by use of diacetoxyiodobenzene, and this can serve as the first step of selective deprotection at *O*-3 of the starting materials.⁹¹

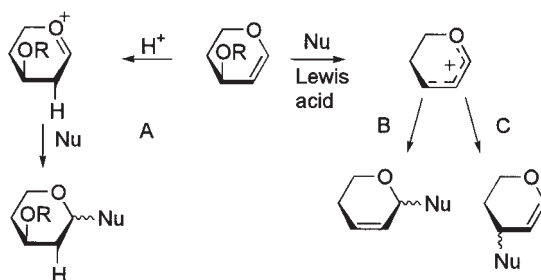
Pyridinium chlorochromate in dichloroethane effects smooth conversion of tri-*O*-acetyl-D-glucal to the unsaturated lactone **79** at 80 °C.⁹²

**75****76** R = H**77** R = Ac**78** R = Bn**79**

c. Substitution Reactions at C-1.—Glycals can undergo direct, base-promoted metal substitution of H-1 and subsequent conversion to C-1-carbon-substituted derivatives. Reactions of this category are treated in [Section II.3.a](#).

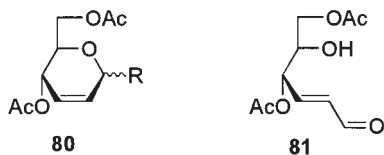
d. Rearrangement Reactions.—Glycals and their *O*-substituted derivatives commonly add alcohols and phenols in the presence of protonic acids to give 2-deoxy glycosidic products, as indicated in [Scheme 7](#), Route A, and as already discussed ([Section II.2.a.i](#)). Their reactions (especially those of *O*-acylated glycals) when activated by Lewis acids are normally quite different, involving loss of the allylic substituents at C-3 to form intermediate delocalized cations from which 2,3-unsaturated glycosides are readily produced in the presence of *O*-nucleophiles ([Scheme 7](#), Route B). With tri-*O*-acetyl-D-glucal and -galactal, α anomers are favored relative to the β by 7:1 and 10:1, respectively.^{5,93,94} It must be stressed, however, that there are occasional exceptions to these generalizations with strong protonic acids and nucleoside bases leading to 2,3-unsaturated nucleoside analogues,⁹⁵ and Lewis acids sometimes giving saturated products ([Section II.2.d.ii](#)). Further exceptions are encountered with *S*- and *N*-nucleophiles that can give products apparently formed by direct displacement of the glycal allylic substituents, as in [Scheme 7](#), Route C (see [Section II.2.d.ii](#)).

In his paper describing the first synthesis of tri-*O*-acetyl-D-glucal (**5**), Emil Fischer noted that, on being heated in water, it apparently loses an acetyl group to give products later identified as the allylically rearranged 2,3-unsaturated free sugars **80** ($R=OH$), which, in the presence of light, isomerize to the *E*-enal **81**.⁹⁶ It seems probable that the presence of **80** and/or **81** in Fischer's tri-*O*-acetal-D-glucal gave rise to the reducing properties that led to the use of the anomalous suffix in the glycal name.⁹⁷ Later, it became evident^{93,94} that this allylic rearrangement reaction can also be used to make analogues of **80** ($R=OH$) having alkoxy (including sugar groups), phenoxy, thio, and some amino groups bonded at C-1, and



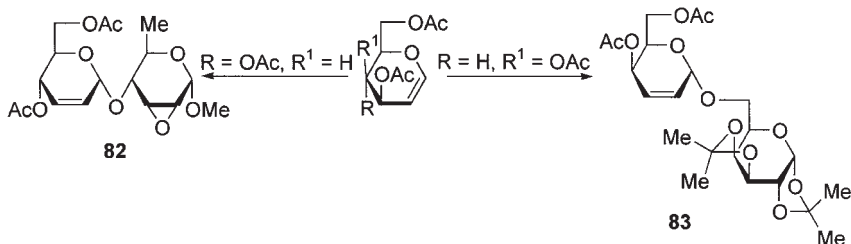
SCHEME 7

also most importantly, C-bonded groups. This has become the main way of making 2,3-unsaturated glycosyl compounds. Importantly, the rearrangement reaction can be used under mild conditions with equimolar proportions of the nucleophiles, and can be applied to some degree with furanoid glycal derivatives, although such starting materials and their products are much less stable than their pyranoid analogues.



(i) **Rearrangement Reactions Involving O-Nucleophiles.**—Tri-*O*-acetyl-D-glucal reacts efficiently with alcohols and phenols to give 2,3-unsaturated glycosides (**80**, R = O-alkyl, O-aryl) without the need for catalysts, but excess of the nucleophiles and temperatures well above 100 °C must be used. In the presence of Lewis acids (often boron trifluoride etherate) and inert solvents, however, the reactions proceed at near ambient temperature and with equimolar proportions of nucleophiles to give good yields of mainly α -glycosides. With tri-*O*-acetyl-D-galactal, however, $\text{BF}_3 \cdot \text{OEt}_2$ is ineffective and tin(IV) chloride is used instead.^{93,94} Presumably the tin salt promotes this reaction through enhanced coordination with the acetoxy group at C-3 as compared with BF_3 , thus enabling the departure of the allylic group without the anchimeric assistance often provided by the *trans*-acetoxy group at C-4 of tri-*O*-acetyl-D-glucal. As shown in Scheme 8, application of this reaction to the coupling of tri-*O*-acetyl-D-glucal or tri-*O*-acetyl-D-galactal with the appropriate alcohols gives the disaccharide derivatives **82**⁹⁸ and **83**⁹⁹ in 71% (α , β , 1:0) and 56% (α , β , 10:1), respectively.

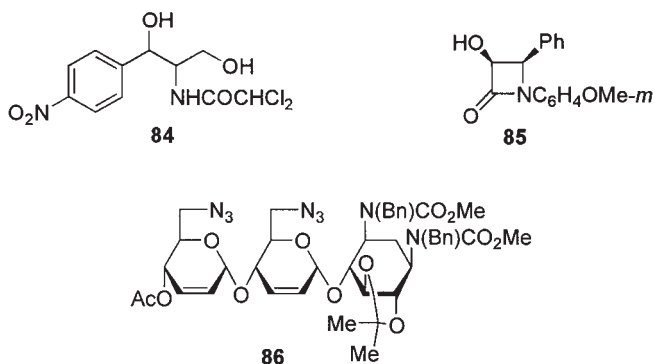
Importantly, this glycosylation reaction can be promoted under nonacidic conditions and its scope is thereby widened. Glycals with allylic hydroxyl



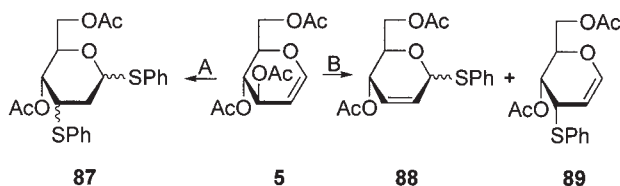
SCHEME 8

groups are activatable with Mitsunobu reagents (Ph_3P , diethyl azodicarboxylate, DEAD)¹⁰⁰ or by use of DDQ¹⁰¹ in lieu of a Lewis acid as catalyst. In the case of the latter promoter, O-3 acylated glycal derivatives also react. Otherwise, the reactions can be conducted under neutral conditions using allylic leaving groups that can be specifically activated under mild conditions. These groups include alkyl- or aryl-thio or pent-4-enoyl moieties that are nucleophilically displaceable with allylic rearrangement by use of iodonium electrophiles as promoters.¹⁰²

As well as being applicable to the glycosylation of monohydroxy compounds, the reaction has been used to disubstitute diols such as chloramphenicol (**84**), to give products of sequential substitution such as **86**, and hence saturated glycosylated compounds. In a different type of application, the resolution of the racemate of compound **85** can be accomplished by glycosylation and separation of the diastereomers to afford the illustrated enantiomer which was required for work on the synthesis of taxol.



(ii) *Rearrangement Reactions Involving S- and N-Nucleophiles.*—With thiols, and in the presence of acid catalysts, glycal derivatives react initially as they do with alcohols to give mainly 2,3-unsaturated thioglycosides (Scheme 7, Route B), but these represent the kinetic products, and at equilibrium the isomeric 3-substituted glycals (Scheme 7, Route C) are favored. This notwithstanding, the thioglycosides are readily available compounds, being formed initially together with only minor amounts of the 3-substituted isomers. For example, the phenylthio glycoside **88** (α isomer) can be isolated in 71% yield together with its β anomer (9%) and the 3-thioglycal **89** (6%) from the reaction of tri-*O*-acetyl-D-glucal and thiophenol in benzene with $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst (Scheme 9, path B). When, however, this reaction is conducted under identical conditions, but with 4 mol% of water present, it changes dramatically, and the products are the four isomers of **87**

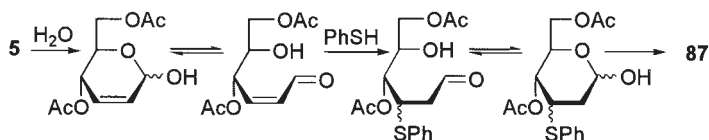


SCHEME 9

(83% isolated, α -ribo, β -ribo, α -arabino, β -arabino, 3:5:5:1) (Scheme 9, path A).¹⁰³ This finding suggests that the glycal may react in the presence of small amounts of water as indicated in Scheme 10, and shows that the rearrangement reactions should be conducted under anhydrous conditions. Reciprocally, the finding of 2-deoxy-1,3-disubstituted saturated products may indicate the presence of water in reactions media, and easily dehydrated alcohols may, therefore, give these spurious compounds.

Azide ions (like the soft thio nucleophiles) used together with boron trifluoride, initially give mainly 2,3-unsaturated glycosyl azides that then equilibrate to give mixtures containing largely 3-azido-3-deoxyglycals. For example, with tri-*O*-acetyl-D-glucal, the percentages of the products at equilibrium are: 3-azido-3-deoxy-D-allal and -glucal (50 and 24%) and 2,3-unsaturated α - and β -glycosyl azides (15 and 11%),¹⁰⁴ it being unclear whether equilibration occurs by reversal to the initially formed 2,3-unsaturated glycosyl carbocations or by intramolecular sigmatropic rearrangements of the kinetic products, the azido group being an ambient nucleophile.

In a similar manner tri-*O*-acetyl-D-glucal with 2,6-dichloropurine in boiling nitromethane with catalytic toluenesulfonic acid initially gives 2,3-unsaturated glycosyl nucleoside analogues, and these also subsequently isomerize to the 3-substituted glycals.¹⁰⁵ The products of the initial step can be obtained, nonetheless, when glycals with enhanced leaving groups at the allylic position are used.¹⁰⁶ Otherwise, *N*-trimethylsilylated thymine with, for example, trityl and lithium perchlorate as catalysts may be used to give 2,3-unsaturated nucleoside analogues.¹⁰⁷ Pyrimidine bases are used less frequently for coupling with glycals, an example, however, being the



SCHEME 10

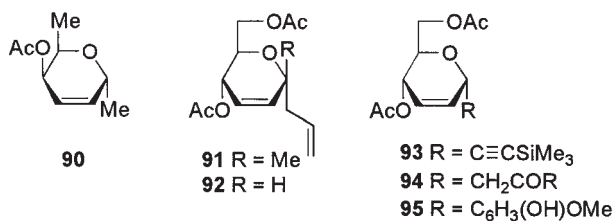
reaction of tri-*O*-acetyl-D-galactal with bis-*O*-(trimethylsilyl)uracil in ethyl acetate with antimony perchlorate as catalyst, which yields an unsaturated uracil nucleoside from which the nucleoside component of blasticidin S (**3**) has been made.¹⁰⁸

(iii) Rearrangement Reactions Involving C-Nucleophiles.—Reagents such as some organometallic compounds, cyanide, various *C*-silylated derivatives, enol ethers and esters, activated aryl and β -dicarbonyl compounds can provide nucleophilic species under the conditions used for the rearrangement reaction and thereby afford 2,3-unsaturated *C*-glycosylic compounds (commonly termed “*C*-glycosides”). Given the range of the foregoing nucleophiles, an extensive set of 2,3-unsaturated *C*-glycosylic products are available; only extremely occasionally have *C*-3-branched-chain glycals been recorded as products.

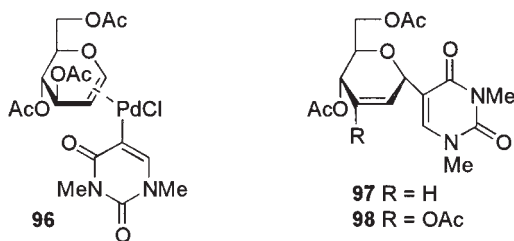
Simple alkylation can be accomplished by use of trialkylaluminums which, with Lewis acids, afford 1-*C*-alkyl products such as **90**, available in 72% yield by reaction between di-*O*-acetyl-6-deoxy-D-galactal and trimethylaluminum in the presence of titanium tetrachloride in dichloromethane at -78°C .¹⁰⁹ Importantly, the reaction can also be applied to 1-alkylglycals, also with high stereoselectivity, so that the doubly substituted compound **91** can, for example, be made by allylation of tri-*O*-acetyl-1-*C*-methyl-D-glucal. Its *C*-1 epimer is available by *C*-methylation of the 1-*C*-allylglucal.¹¹⁰

Some of the most useful 2,3-unsaturated *C*-glycosyl derivatives are the allyl compounds such as **92**, made by use of allyltrimethylsilane, and a notable feature of this compound is that it can be produced directly from tri-*O*-acetyl-D-glucal with DDQ as promoter.¹¹¹ A further surprising feature of this *C*-allylation procedure, however, is its applicability to glycals that are not *O*-substituted. Reactions are carried out in dichloromethane–acetonitrile at low temperatures with trimethylsilyl triflate as catalyst, and almost quantitative yields of 2,3-unsaturated *C*-allyl glycosyl compounds are recorded, with the α anomers being formed almost exclusively.¹¹²

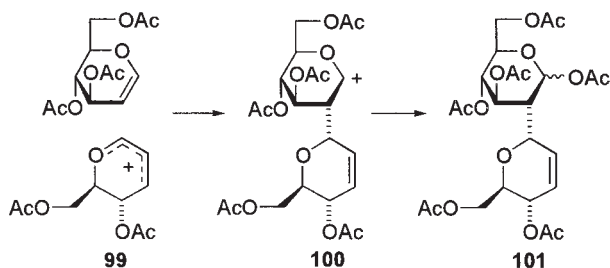
Other examples of the many 2,3-unsaturated *C*-glycosides to have been made efficiently from tri-*O*-acetyl-D-glucal are **93** made with bis(trimethylsilyl)acetylene,¹¹³ glycosylmethyl ketones **94** with enol silyl ethers of the corresponding methyl ketones,¹¹⁴ and the aryl compound **95** with *p*-methoxyphenyloxymagnesium bromide under ultrasonic conditions.¹¹⁵ Otherwise, aryl compounds such as **95** can be prepared from the corresponding *O*-glycosides by rearrangement that occurs on extensions of the conditions of synthesis of the latter.¹¹⁶



An entirely different approach to 2,3-unsaturated *C*-glycosides involves the intermediacy of glycal organopalladium(II) adducts such as **96** made by use of palladium compounds derived from corresponding organomercurials. Treatment of the illustrated adduct with triphenylphosphine gives a covalent, saturated C-2-palladium *C*-glycoside, which upon treatment with aqueous sodium hydrogen carbonate affords compound **97** almost quantitatively. When, however, the C-2-palladium adduct is simply heated, *syn*-elimination of a palladium hydride species occurs to give the 3-acetoxyalkene **98**.¹¹⁷ Related furanoid *C*-glycosides can be made similarly.¹¹⁸

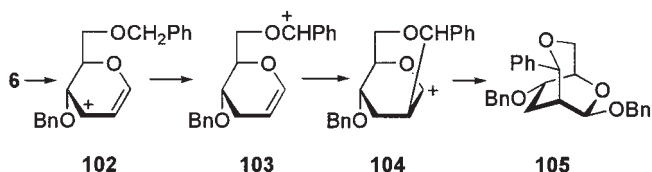


(iv) Other Features and Examples of Rearrangement Reactions.—While a high proportion of the reactions of glycals and their derivatives that result in 2,3-unsaturated glycosyl compounds are straightforward, others illustrate unusual fates experienced by the ionic intermediates involved or constitute adaptations of the basic process. For instance, generation of intermediate ion **99** from tri-*O*-acetyl-D-glucal (**5**) can result in addition to its parent glycal to give the intermediate **100**, and subsequently the *C*-linked dimeric compounds **101** (Scheme 11). Such disaccharides have been recognized as byproducts of several relevant reactions of esterified glycals involving nucleophiles that bond to C-1. In the absence of such nucleophiles, however, dimer **101** has been made in 61% yield (α , β ratio 1.5:1) by treatment of tri-*O*-acetyl-D-glucal with acetyl perchlorate in dichloromethane at -78°C . Tri-*O*-acetyl-D-galactal gives 77% of the analogous α,α -linked dimer as the exclusive product.¹¹⁹



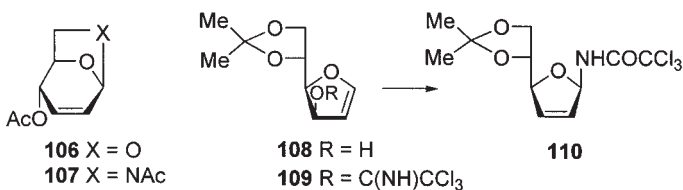
SCHEME 11

In the case of tri-*O*-benzyl-D-glucal, entirely different chemistry is observed, with the initially formed cation **102** abstracting a hydride ion from the O-6 benzyl group to give the 3-deoxy species **103**. Intramolecular addition to C-2 affords **104** and the initially cleaved benzyloxy group adds to C-1 to give the unusual bicyclic **105** in 45% yield (Scheme 12).¹²⁰

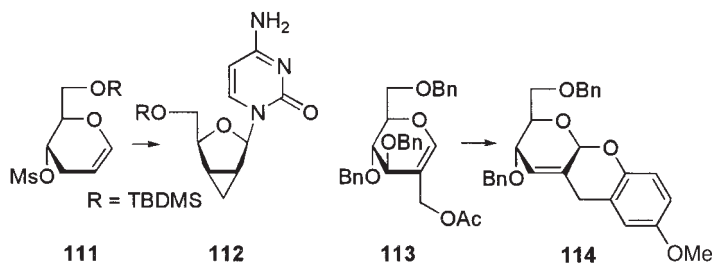


SCHEME 12

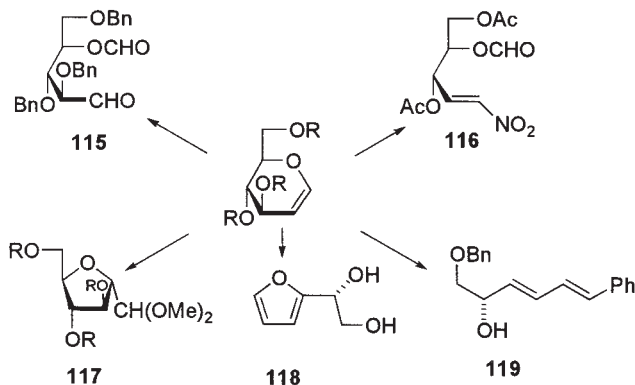
The allylic rearrangement reaction of glycals can proceed intramolecularly with, for example, 3,4-di-*O*-substituted hexose-derived glycals affording high yields of 1,6-anhydrides such as **106** in the presence of Lewis acids,¹²¹ and the amido analogue **107** is produced when 6-acetamido-3,4-di-*O*-acetyl-6-deoxy-D-glucal is treated with $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ in acetonitrile.¹²² Several glycal derivatives containing more complex nucleophilic functions able to attack at C-1 are known. Thus, compound **108**, after conversion to its sodio derivative, reacts with trichloroacetonitrile to give the unstable trichloroacetimidate **109** which spontaneously undergoes [3,3]-sigmatropic rearrangement to afford compound **110** in 78% yield.¹²³



Other unusual relevant reactions involve glycols with “modified leaving groups.” Compound **111**, with a homoallylic mesylate, reacts with a pyrimidine base in the presence of ethylaluminum dichloride to give the cyclopropacytidine nucleoside **112** and its α anomer in equal proportions (81%).¹²⁴ Additionally, the modified glycol **113**, with an allylic leaving group in the branched chain, reacts with *p*-methoxyphenol in the presence of Lewis acids to give the *exo*-methylene *O*-glycoside which undergoes aromatic electrophilic substitution with displacement of the C-3 benzyloxy group to produce the tricyclic product **114**.¹²⁵



e. Other Reactions.—Oxidations of glycols and their *O*-substituted derivatives to the corresponding conjugated 3-uloses, separately to 2,3-unsaturated aldono-lactones (Section II.2.b), and *cis*-hydroxylations of the double bonds (Section II.2.a.ii) have already been referred to, and several other dihydroxylation methods have afforded parent aldoses or their derivatives.⁵ Ozonolysis represents a further oxidative process by which, for example, tri-*O*-benzyl-D-glucal is converted almost quantitatively into the D-arabinose 4-formyl ester **115** (Scheme 13),¹²⁶ and provides a method



SCHEME 13

for descending the aldose series by one carbon atom to give specifically substituted products. A related and unusual reaction occurs when *O*-acetylated glycals (but not analogues with ether groups at C-3) are treated with trifluoroacetic anhydride and dry ammonium nitrate followed by a basic, aqueous workup to give nitroenes such as **116**.¹²⁷

When *O*-alkylated or *O*-acylated D-glucals are heated in 9:1 acetonitrile–methanol with thallium nitrate trihydrate, ring contraction occurs to give compounds **117** in about 50% yield following, it may be assumed, addition of the metal ion at C-2 and methoxyl at C-1 to lead to intermediates that ring contract to the 2,5-anhydro products.¹²⁸

While D-glucal reacts with mercury(II) sulfate in strong acid solution to give 2-(D-*glycero*-1,2-dihydroxyethyl)furan (**118**) as the major product, neither reagent is desirable, especially for large-scale work, and alternative conditions have been developed. Samarium triflate in acetonitrile at 80 °C under an inert atmosphere gives a 70% yield,¹²⁹ and even higher yields are obtained when indium trichloride is used as catalyst. Under these conditions di-*O*-acetyl-L-rhamnal does not give an analogous product because the expected furan undergoes cyclotetramerization.¹³⁰ Quite different types of dienes are produced on treatment of glycal ethers with aryl Grignard reagents in the presence of nickel(0) catalysts, tri-*O*-benzyl-D-glucal giving, for example, compound **119** in 62% yield together with small proportions of the 2*Z*, 4*E* isomer.¹³¹

3. Glycals with Substituents on the Double Bonds

The development of methods for making glycals with substituents on C-1 and/or C-2 has extended the synthetic uses of unsaturated sugar compounds for the production of carbohydrate analogues and noncarbohydrate products. For many years the only well-known substituted compounds of this category were those with acyloxy groups at C-2, made by elimination of hydrogen halide from peracylated glycosyl halides. An extensive range of vinyl-substituted derivatives has now been described.

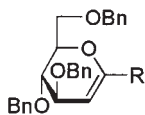
a. Glycals with Substituents at C-1.—Compounds with several types of substituents at C-1 are known, the most useful having C–C bonded groups. These can be made by a variety of methods including formation of C-1 carbanionic glycal species, followed by their reaction with electrophiles (or analogous palladium-catalyzed processes), eliminations from C-glycosylic compounds or, unusually, by concurrent eliminations and new C-1–C bond formations.

A key development came in 1986 with the establishment of methods for generating C-1 lithiated and stannylated species such as **120** and **121**.^{132–134}

Direct C-1 deprotonation–lithiation occurs on treatment of the *O*-benzylated or -silylated glycols with strong bases such as *tert*-butyllithium at low temperatures, and the vinylolithiums (such as **120**) can subsequently be stannylated with tributylstannyl chloride.¹³⁵ Otherwise, compound **121** can be produced from *S*-phenyl tetra-*O*-benzyl-1-thio- β -D-glucopyranoside via sulfone **122** by treatment with tributylstannane and a radical initiator.¹³²

The lithiated species **120**, also obtainable by metal exchange of the tin analogues, reacts with electrophiles such as methyl halides, benzaldehyde, or dimethyl carbonate to give products such as **123–125**, respectively.^{132,133} 1-*C*-Aryl compounds¹³⁵ are also derivable from the 1-lithioglycols on reaction with *p*-benzoquinones and reduction of the resulting quinonoid adducts,¹³⁶ or by Stille coupling of 1-stannyl derivatives with aryl halides catalyzed by palladium(0).¹³⁷ Two features of the latter approach are that the strategy is applicable to furanoid glycols,¹³⁸ and that the 1-arylglycols may be converted to corresponding aryl *C*-glycosides by hydroboration.¹³⁹

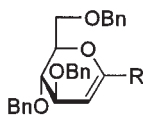
An analogous but mechanistically different approach to 1-*C*-substituted glycols involves the use of the glycal-1-yl phosphate **126** made from the 2-deoxygluconolactone by treatment with strong base and trapping of the resulting enolate with phosphoryl chloride. With tributyl(vinyl)tin in the presence of palladium(0) and lithium chloride, the phosphate gives the conjugated diene **127** in 75% yield.¹⁴⁰



120 R = Li

121 R = SnBu₃

122 R = SO₂Ph



123 R = Me

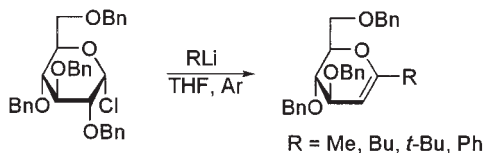
124 R = CH(OH)Ph

125 R = CO₂Me

126 R = OP(O)(OPh)₂

127 R = CH=CH₂

The second approach to 1-*C*-substituted glycols involves introduction of the double bond to saturated compounds already bearing C-substituents at C-1. For example, base-catalyzed elimination of benzoic acid from tri-*O*-benzoyl- β -D-xylopyranosyl cyanide gives the 1-cyanoglycal,¹⁴¹ and further examples of groups that can be found as substituents at C-1 of glycols are: CO₂Me (glycols derived from cyclic 3-deoxy-2-ulonic acid methyl esters),¹⁴² CH₂OAc (glycols derived from fructopyranosyl bromides with good leaving groups at C-3)¹⁴³, and C \equiv CSiMe₃ (from 2-deoxyaldonolactones by Grignard addition reaction followed by dehydration).¹⁴⁴

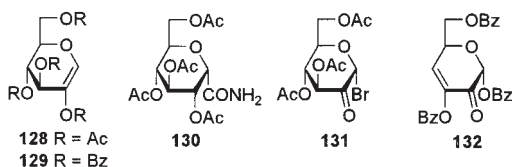


SCHEME 14

The third and unusual approach to C-1–C-substituted glycals, which involves simultaneous introduction of a C-nucleophile at C-1 and elimination, is illustrated in [Scheme 14](#). Treatment of ether- or acetal-protected glycopyranosyl chlorides with methyl-, butyl-, or phenyl-lithiums in THF under argon at room temperature or below, gives moderate yields of the C-1 substituted compounds.¹⁴⁵

b. Glycals with Substituents at C-2.—Most common amongst compounds of this group are the “2-hydroxyglycals,” which, because they are enols, are known only as their *O*-substituted derivatives readily available by removal of hydrogen halide from *O*-acylated glycosyl halides such as **7**. Elimination is facilitated by conversion of the more accessible bromides into iodides prior to treatment with bases such as diethylamine in acetonitrile.⁵ Otherwise, DBU may be used in DMF. Best-known compounds of the series are the D-glucose-derived **128** and **129**. A palladium-catalyzed elimination from *O*-benzyl glycosyl mesylates has been shown to be a convenient method for the formation of tetra-*O*-benzyl analogues.¹⁴⁶ By this strategy 2,3,4,6-tetra-*O*-benzylglucose, for example, is treated with methanesulfonic anhydride to provide the glucosyl mesylate, and *in situ* treatment with Pd(PPh₃)₄ results in metal insertion into the C-1–mesylate bond. Elimination of a palladium hydride species then occurs to afford the *O*-benzylated “hydroxyglycal” in yields up to 87%.

Acetate **128** undergoes some direct addition reactions such as acetone-initiated photochemical addition of formamide to give the anhydroheptonamide **130** in 50% yield.¹⁴⁷ Many adducts, however, are relatively unstable, especially those with halogen substituents at C-2, which have a strong tendency to undergo further reaction to produce C-2 carbonyl compounds. For instance, **128** gives the 2-ulosyl bromide **131** on brief treatment with *N*-bromosuccinimide in methanol.¹⁴⁸ Compounds of this latter type (especially *O*-benzyl-protected analogues) are useful glycosylating reagents for the synthesis of β -mannopyranosides.¹⁴⁹ Chlorination of benzoate **129**, and hydrolysis of the adduct, affords enone **132** in good yield by way of a 1,2-benzoxonium-2-chloro intermediate, which hydrolyzes to a 2-ketone prior to undergoing β -elimination of benzoic acid.¹⁵⁰

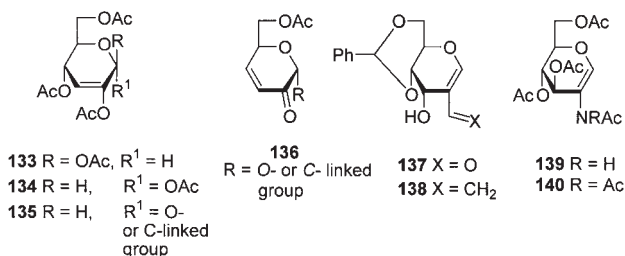


Like *O*-acylated glycals the 2-acyloxy analogues take part in allylic rearrangement reactions, the simplest of which is isomerization. Thus, acetate **128** undergoes specific [3,3]-sigmatropic isomerization on heating in an inert solvent to give β ester **133**, while heating in acetic acid causes rearrangement to a mixture of the α and β anomers **134** and **133** in an equilibrium ratio of 3.3:1.¹⁵¹ With various *O*-¹⁵² and *C*-¹⁵³ nucleophiles, in particular, and in the presence of Lewis acids, the first products obtained from “2-hydroxyglycal” esters are mainly the analogues of those formed from *O*-acylated glycals, namely, 2,3-unsaturated α -glycosyl compounds such as **135**. These compounds have a propensity to undergo cleavage of the enol esters to give the 3-deoxy-2-ketones and then, by β -elimination, the 3,4-dideoxyenones **136**.

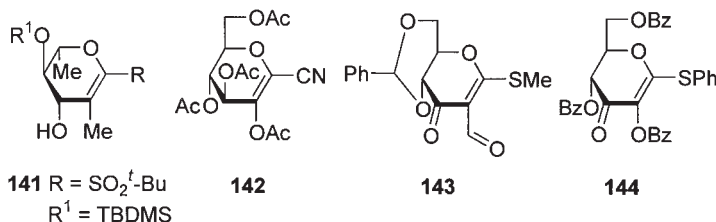
Glycal derivatives with C-2-bonded alkyl groups can be made from 2-alkyl-2-deoxy-glycosyl compounds by standard elimination reactions,¹⁵⁴ likewise analogues with masked formyl groups at C-2 such as 1,3-dithian-2-yl¹⁵⁵ or methoxymethylene¹⁵⁶ readily afford compounds such as **137** on demasking, and these on methylenation give the corresponding conjugated enes such as **138**.¹⁵⁶ An entirely different approach to 2-*C*-formylglycals involves reaction of *O*-ether-protected glycals with DMF and phosphorus oxychloride followed by basic hydrolysis (Vilsmeier–Haack reaction).¹⁵⁷

Glycals with C-2 substituents that have unsaturated, electron-withdrawing character undergo nucleophilic addition at C-1 and are therefore potential glycosylating agents. The use of tri-*O*-benzyl-2-nitro-D-galactal in the synthesis of 2-amino-2-deoxy- α - and β -galactosides by this approach has already been mentioned (Section II.2.a.i).

The 2-*N*-acetyl **139** and 2-*N,N*-diacetyl **140** analogues of the tetra-*O*-acetyl-2-hydroxyglucal **128** are known compounds¹⁵⁸ which have not been fully exploited.



c. Glycals with Substituents at C-1 and C-2.—Compounds of this class are not well known, but there are examples, such as **141**–**144** that are made, respectively, by direct *C*-methylation of the 1-sulfonylated glycal,¹⁵⁹ by elimination of hydrogen bromide from the 1-cyanoglycosyl bromide,¹⁶⁰ by a rearrangement which accompanies acid-catalyzed hydrolysis of the analogous methyl 2-deoxy-2-di(methylthio)methylene α -glycoside,¹⁶¹ and directly and in high yield from the phenyl 1-thio- β -D-glucoside tetrabenzoate simply by heating under reflux under a heat lamp with *N*-bromosuccinimide in carbon tetrachloride.¹⁶²



III. PYRANOID AND FURANOID 2- AND 3-ENES

Unsaturated cyclic sugar derivatives having 2,3- or 3,4-double bonds are also an extensive class of compounds widely used as synthetic building blocks and as nucleoside analogues. Both synthetic and naturally occurring nucleosides of this type, such as **1** and **3**, show important biological properties.

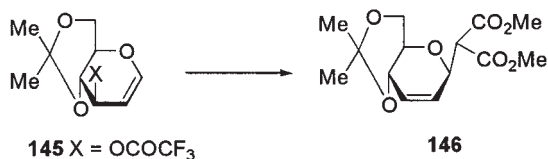
Relevant pyranoid and furanoid compounds (with the exception of the furanoid 3-enes that, as enol ethers, are noted in [Section IV.1](#)) have “isolated” double bonds in the sense that they are not components of vinyl ethers. In consequence their chemistry is distinct from that of the glycals and their derivatives; in particular, their addition reactions are seldom regioselective as are those of the glycals.

1. Preparation

a. From Carbohydrate Sources.—Perhaps the most widely used and facile method for the formation of 2,3-unsaturated derivatives involves nucleophilic displacements, with allylic rearrangement, applied to glycal derivatives under Lewis-acid catalysis as described in [Section II.2.d](#). The method is of value for introducing *O*-, *N*-, *S*-, and *C*-linked groups at C-1. A limited related route to 3,4-enes from 2,3-unsaturated derivatives involves intramolecular allylic rearrangement processes. For example,

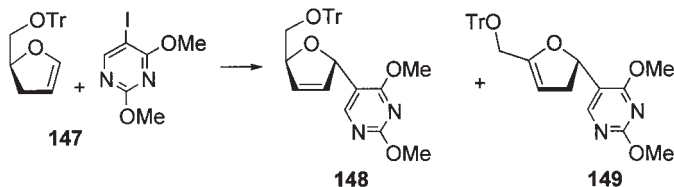
4-thiocyanato-2-enes isomerize thermally to the 2-isothiocyanato-3-enes (Section III.2.d). Reciprocally, in some cases, 3-enes can be analogously rearranged to 2-enes.

With the propensity of substrates with allylic functionality to undergo palladium(0)-catalyzed reactions with nucleophiles, a further method for the conversion of glycal derivatives to 2,3-unsaturated glycosyl compounds—especially C-glycosides—is available as noted briefly in Section II.2.d.iii. Despite evidence provided in that section, glycal derivatives with acyloxy allylic groups can be unreactive, but in such circumstances use of compounds with better allylic leaving groups can lead to useful products. For example, the glycal trifluoroacetate **145** gives the β -C-glycosyl product **146** stereospecifically in 52% isolated yield, along with minor amounts of the product of trifluoroacetate hydrolysis, on treatment with potassium dimethyl malonate in the presence of catalytic amounts of bis(dibenzylideneacetone)Pd(0). The stereochemistry of the process is in accord with the usual double-inversion mechanism associated with this kind of reaction, and the substrate undergoes nucleophilic attack at the anomeric carbon and not at C-3.¹⁶³

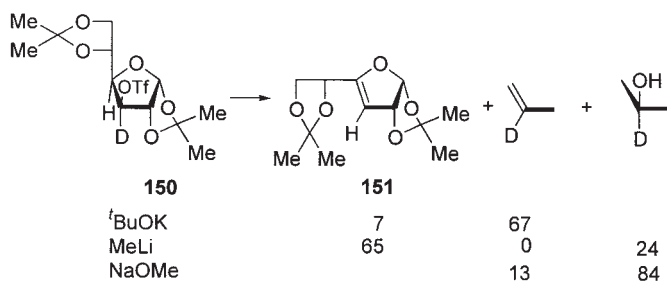


Heck reaction of 5-iodo-2,4-dimethoxypyrimidine and the furanose 3-deoxyglycal **147** with catalytic quantities of palladium acetate gives a mixture of the 2,3- and 3,4-enes **148** and **149** (Scheme 15). With triphenylarsine also present the latter product is favored, whereas with triphenylphosphine the 2-ene is produced without its isomer.¹⁶⁴ Further examples of this type of chemistry have been reviewed by Daves.¹¹⁸

The other main approach to the synthesis of compounds with isolated double bonds is based on elimination reactions applied to



SCHEME 15



SCHEME 16

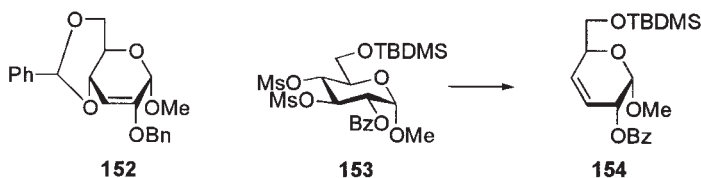
monohydroxy-, vicinal dihydroxy-, and epoxy-starting materials.⁵⁻⁷ Compounds having single alcohol centers with neighboring methylene groups can usually be converted into the enes with double bonds between the respective carbon atoms by base treatment of derived sulfonate esters or by pyrolysis of xanthates. For example, 2'-deoxyfuranosyl nucleosides can readily be converted to the 2',3'-unsaturated analogues, such as **1**, in this way.

With vicinally related hydroxysulfonates, simple β -eliminations are often thwarted by epoxide formation.¹⁶⁵ If elimination of sulfonic acid does occur, reactive ketones are formed, and when the functions that neighbor the sulfonates are alkoxy groups, single alkenes are still seldom obtainable. An exception is with the formation of the furanoid 3-ene **151**, produced in good yield from triflate **150** under basic conditions. Even this reaction, however, is not straightforward, as is evidenced by the percentages of products formed from the deuterium-labeled substrate (Scheme 16) on treatment with different bases. With potassium *tert*-butoxide H-4 is the proton preferentially abstracted (as expected), but when the base is methyllithium H-3 is preferentially removed, and the elimination proceeds by way of a carbene intermediate. On the other hand, sodium methoxide primarily attacks at sulfur in the ester substituent and gives the 3-ol as the main product. Mixed products containing the 2- and 3-enes are formed by elimination with methyllithium of triflic acid from methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-triflyl- α -D-glucopyranoside. While the former gives similar proportions of the 2- and 3-enes, the *allo*-isomer affords **152** with high selectivity.¹⁶⁶

Other methods used for effecting elimination of water from monohydroxy compounds include treatment with thionyl chloride in pyridine¹⁶⁷ and sulfonylation followed by treatment with tetrabutylammonium fluoride-potassium fluoride¹⁶⁸ or DBU.¹⁶⁹

Vicinal diols are readily converted into alkenes by well-established methods,⁵⁻⁷ often by the Tipson-Cohen procedure involving the treatment

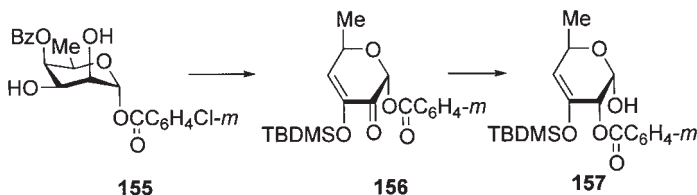
of derived disulfonates in boiling DMF with sodium iodide and zinc. In this way, for example, dimesylate **153** is efficiently converted to the alkene **154**,¹⁷⁰ and both *cis*- and *trans*-related diesters may be used as starting materials. However, diols themselves on treatment with triphenylphosphine, imidazole, and iodine,¹⁷¹ or with triphenylphosphine and triiodoimidazole,¹⁷² undergo the required eliminations as do derived dioxanthate esters by reductive radical cleavage. By a related free-radical process, the diesters of 5'-*O*-substituted ribonucleosides afford the 2'-alkenes in near-quantitative yield on treatment with diphenylsilane and the radical initiator 2,2'-azobisisobutyronitrile in refluxing toluene.¹⁷³



Cyclic orthoesters derived from *gem*-diols offer a further route to alkenes. As part of a three-step conversion, they may be ring opened with hydrobromic acid to give *O*-acyl bromodeoxy compounds that undergo reductive elimination with copper–zinc. In this way, unsaturated nucleosides have been made by way of mixed 2'/3'-bromo-2'/3'-deoxy-3'/2' carboxylates.¹⁷⁴ A more direct route to alkenes from cyclic orthoesters involves heating in acetic anhydride together with zirconium oxide.¹⁷⁵

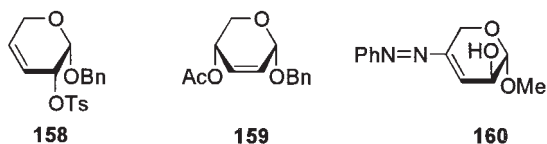
An entirely different approach to the introduction of isolated double bonds is illustrated by the selective silylation of the 3-hydroxy group of **155** and Swern oxidation at C-2 to give **156** following spontaneous elimination. Final conversion of the enone to the free sugar **157** is accomplished by carbonyl reduction that induces an ester migration (Scheme 17).¹⁷⁶

Epoxides and episulfides are commonly used as precursors of alkenic derivatives, and the analogous epimines undergo elimination on diazotization. The strategy with epoxides normally involves nucleophilic ring opening of the three-membered rings to generate hydroxy products which, on derivatization, can undergo the required eliminations.^{5–7} For example,



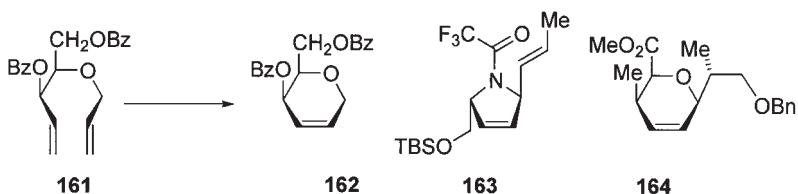
SCHEME 17

compounds **158** and **159** are available from corresponding 3,4- and 2,3-epoxides, respectively, by treatment with sodium iodide and acetic acid, and subsequent reaction of the resulting iodoalcohols with phosphorus oxychloride in pyridine.¹⁷⁷ An entirely different approach which is mild, direct, and free radical in character simply involves treatment of epoxides with bis(cyclopentadienyl)titanium(III) chloride in THF under an inert atmosphere at room temperature.¹⁷⁸ Appropriate ketoepoxides can also give access to substituted alkenes. For example, treatment of methyl 2,3-anhydro- β -L-*erythro*-pentopyranosid-4-uloside with phenylhydrazine gives the phenylazoalkene **160** in 70% yield.¹⁷⁹

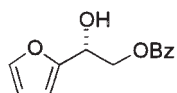
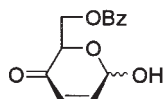


b. From Noncarbohydrate Sources.—A limitation in the foregoing methods of synthesis of unsaturated compounds based on the use of sugars is their reliance on the readily available members of the series in their naturally occurring forms which, with the exception of L-arabinose, are the D isomers. Methods that can be applied to both enantiomers of target substances are therefore of value, and several have been developed from noncarbohydrate sources. Relevant work on making carbohydrates from noncarbohydrate starting materials has been reviewed.^{180,181}

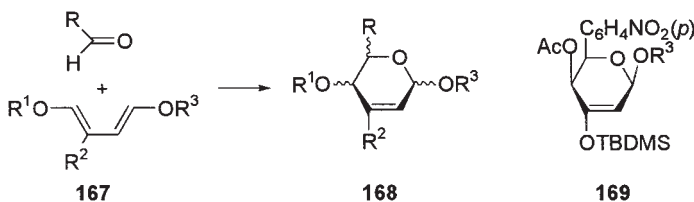
Ring-closure metathesis has become an important tool in organic synthesis and has been applied extensively in carbohydrate chemistry, including to the synthesis of glycals (see Section II.1.a) and other unsaturated sugar derivatives.^{182,183} For example, Grubbs' catalyst causes the cyclization with loss of two carbon atoms of diene **161**, which is assembled by asymmetric aldol procedures, to the 1,5-anhydropyranose compound **162** in 90% yield. The iminosugar **163** and C-glycosyl compound **164** are other examples of unsaturated sugar derivatives that can be made by this approach.



A very simple method for producing 2,3-unsaturated 4-ulopyranose compounds, for example **166**, is from monosubstituted furans, such as **165**. These can be made readily in enantiomerically pure form either from glycals via the corresponding diol **118**¹⁸⁴ (see Section II.2.e), or from simple furans derived from non-carbohydrate sources. For example, ethyl 2-furan-carboxylate condensed with the anion derived from enantiomerically pure methyl *p*-tolylsulfoxide gives a β -ketosulfoxide, that can be reduced selectively and hydrolyzed to **165**.¹⁸⁵ Treatment of this product with bromine in methanol, followed by mild acid hydrolysis, gives the enantiomerically pure enone **166**. From 2-(hydroxymethyl)furan analogues, but racemic, pentopyranose enones can be made.¹⁸⁶

**165****166**

A further means of access to unsaturated carbohydrates from nonsugars is by application of the hetero-Diels–Alder cycloaddition reaction between substituted-1,3-dienes (**167**) and aldehydes to give dihydropyrans (**168**). This process can be promoted simply by heating,¹⁸⁷ by use of high pressure¹⁸⁸ or by Lewis-acid catalysis.¹⁸⁹ For the synthesis of enantiomerically pure products, dienes bearing chiral auxiliary groups can be employed. For example, compound **167** ($R^1 = \text{Ac}$, $R^2 = \text{OTBDMS}$, $R^3 = \text{tetra-}O\text{-acetyl-}\beta\text{-D-glucopyranosyl}$) gives **169** ($R^3 = \text{tetra-}O\text{-acetyl-}\beta\text{-D-glucopyranosyl}$) with good selectivity when condensed with *p*-nitrobenzaldehyde in the presence of a Lewis acid, the new dihydropyran having the absolute and relative stereochemistry shown.¹⁹⁰ Otherwise, for reactions of this type, impressive enantiomeric excesses (ee's) as high as 99% have been obtained using chiral catalysts such as copper(II) bisoxazolines,¹⁹¹ $[\text{Pd}(\text{S-BINAP})(\text{PhCN})_2(\text{BF}_4)]_2$,¹⁹² titanium BINOL complexes¹⁹³ or chiral polybinaphthyl-aluminum complexes.¹⁹⁴

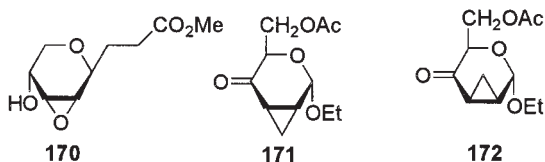
**167****168****169**

2. Reactions

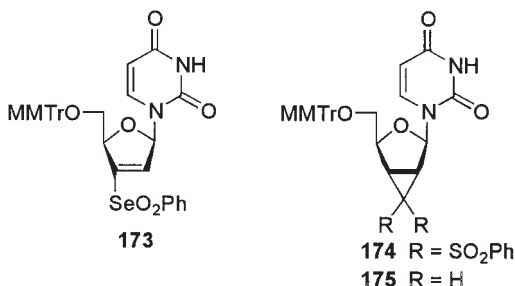
Compounds with isolated double bonds, such as the common 2,3-unsaturated pyranoid derivatives, undergo standard alkene addition reactions.⁵⁻⁷ A significant feature of these, however, is their potential poor regio- and stereo-selectivity, since any unsymmetrical reagent that adds may give up to eight possible products, and means of decreasing this number are often required. For this reason, reactions such as hydroxylations, which are limited to giving four possible products and epoxidations (two products) are preferred processes, and intramolecular addition reactions with their in-built specificities have ultimate attraction. Alternatively, functionality that polarizes the alkene groups, such as conjugated carbonyl groups or nitro substituents, when used, often lead to high regio- and stereo-selectivity.

a. Oxygenations and Other Simple Additions.—*cis*-Hydroxylation of the alkenes with hydrogen peroxide and osmium tetroxide normally occurs from the sterically more accessible side of the sugar rings, O-protected α -D-*erythro*-hex-2-enopyranosides, for example **82**, giving access to mannosides as main products. Applied to the same class of alkenes *cis*-oxyamination with Chloramine T and osmium tetroxide (Sharpless reagent) gives the *manno*-3-deoxy-2-hydroxy-3-tosylamino and the 2-deoxy-3-hydroxy-2-tosylamino adducts in the ratio 2:1.¹⁹⁵ Epoxidation is also readily conducted, with compounds having allylic hydroxyl groups directing the incoming oxygen atoms to approach the double bonds in a *syn* manner, the opposite being the case when the hydroxyl groups carry substituents. Hence, α -*erythro*-hex-2-enosides give predominantly *manno* epoxides when O-4 is protected and *allo* isomers when it is not.¹⁹⁶ The D-xylose-based epoxide **170** is obtained from the corresponding hydroxyalkene, this strategy having led to the synthesis of leukotriene D₄ analogues.¹⁹⁷

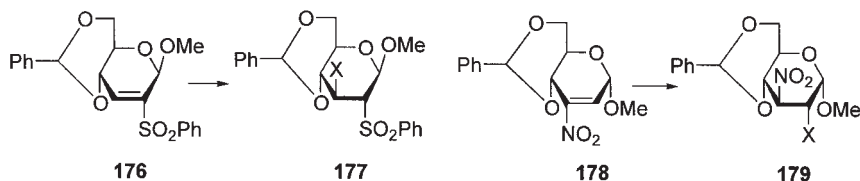
Cyclopropanation reactions have generated appreciable interest since the products have potential for chemical manipulation and as enzyme inhibitors.⁶⁰ A notable early finding is that addition at either side of a double bond can be induced by manipulation of the structures of the substrates. For example, compound **171** is obtained from ethyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside by Simmons-Smith cyclopropanation (diiodomethane and Zn-Cu couple) followed by conversion of the C-4 group from an ester to a carbonyl. On the other hand, the substrate with a carbonyl group instead of the ester at C-4 cyclopropanates to give the α -*lyxo* product **172**.¹⁹⁸



Electron-deficient alkenes, either these with conjugating substituents or of enones, undergo Michael-like additions with regiospecific introductions of the nucleophiles, and this approach has been successful for the formation of cyclopropyl derivatives—notably from some nucleosides. An example involves the addition of the anion of bis(phenylsulfonyl)methane to the phenylselenone **173** which gives the adduct **174** in 35% yield. This reaction presumably occurs by Michael addition to C-2'; followed by S_N2 ring-closure reaction at C-3' with displacement of phenylselenenic acid. Reductive desulfonylation affords the 2',3'-dideoxy-2',3'-cyclopropayuridine **175**.¹⁹⁹

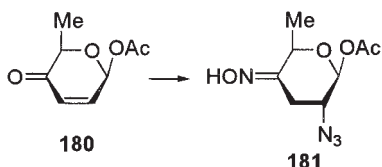


Related reactions of the substituted alkenes **176** and **178** with basic nucleophiles such as ammonia occur at C-3 and C-2, respectively, to give the thermodynamically favored *gluco* adducts **177**²⁰⁰ and **179**.²⁰¹ Alternatively, the nitroalkene **178**, under neutral or weakly acid conditions, adds nucleophiles such as hydrazoic acid, hydrogen cyanide–potassium cyanide, or purine bases at C-2 to give the α -*manno* products.²⁰¹

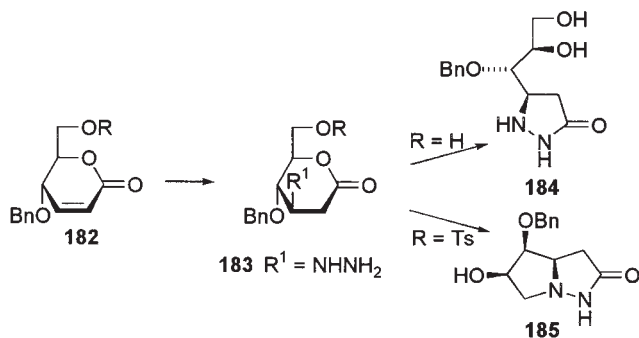


A powerful example of the use of conjugated enones in the synthesis of 2,4-difunctionalized compounds, such as 2,4-diamino-2,3,4,6-tetra-deoxyhexoses of the kind found in several antibiotics, is illustrated by

the conversion of the 2-ene-4-ulose derivative **180** into compound **181** in 70% yield by a “one-pot” procedure. Initially, sodium azide in THF-acetic acid is added to effect the addition of azide at C-2, and this is followed by hydroxylamine hydrochloride and sodium acetate to afford the illustrated oxime, from which 2,4-diaminohexoses are obtainable.²⁰² Alternatively, unsaturated aldonolactones can give adducts



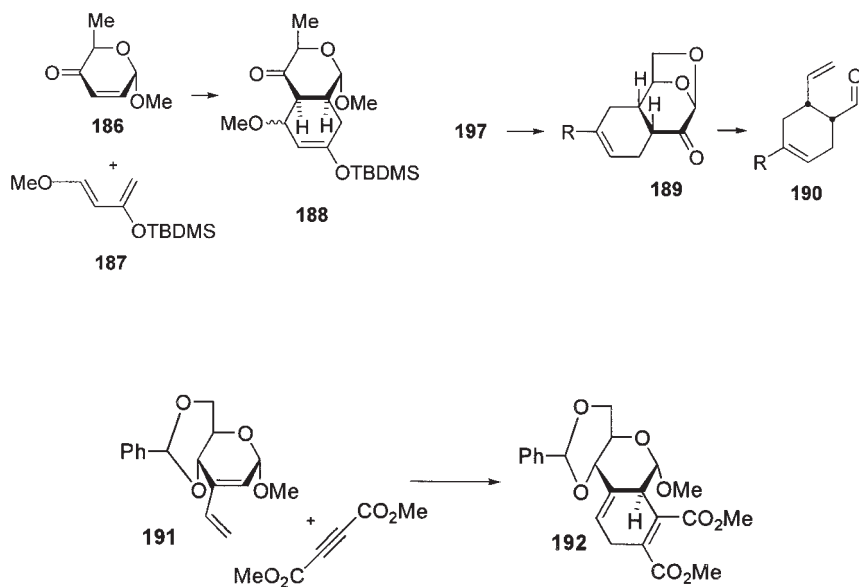
that react further by processes involving the lactone carbonyl groups. Thus, benzyl ether **182** ($R = H$) with hydrazine gives the adduct **183** ($R = H$), which reacts intramolecularly to form the pyrazolidin-3-one **184**, and when the starting material has a leaving group at C-6 such as **182** ($R = Ts$) further reaction takes place to give the bicyclic **185** (Scheme 18).²⁰³



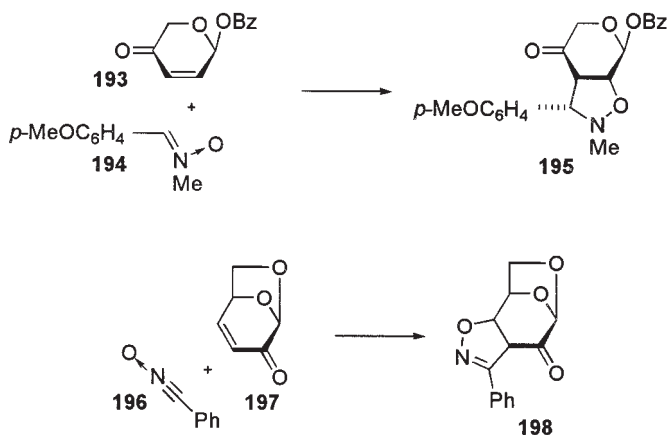
SCHEME 18

b. Intermolecular Cycloaddition Reactions.—There are few, if any, records of carbohydrate derivatives with isolated double bonds taking part in Diels-Alder reactions.²⁰⁴ The opposite is the case, however, with compounds containing enone functions which act as good dienophiles. For example, enone **186**, on reaction with Danishefsky diene **187**, gives exclusively the β -adducts **188** in 93% yield,²⁰⁵ and likewise the 3-en-2-enone “levoglucosenone” **197**, heated with 1,3-butadiene or its 2-substituted derivatives, yields adducts **189** ($R = H, Me, Ph$, for example). These lose carbon dioxide on irradiation in benzene with a high-pressure mercury arc under nitrogen

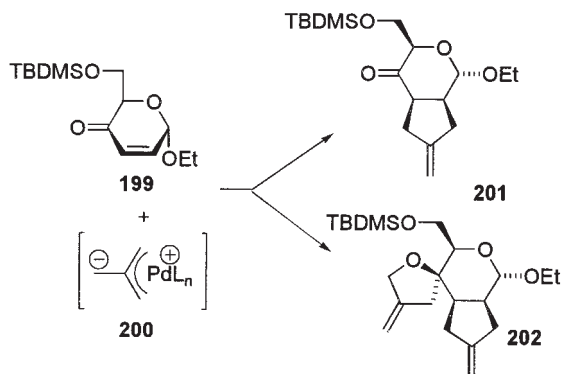
to give the specifically substituted and enantiomerically pure cyclohexanes **190**.²⁰⁶ When the double bonds of 2-enes are activated by substitution of a formyl group at C-2 or C-3, normal Diels–Alder additions can occur. However, when a vinyl substituent is present at one of these positions the role of the carbohydrate in the reaction is reversed, diene **191**, for example, giving the adduct **192** on heating with dimethylacetylene dicarboxylate.²⁰⁷



Carbohydrate-conjugated enones are also subject to 1,3-dipolar cycloaddition reactions that lead to stereochemically defined products,^{208–210} enone **193**, for example, producing the isoxazolidine **195** (70%) on treatment with nitron **194**.²⁰⁸ The stereochemistry of the additions depend on the configurations of the nitrones and dipolarophiles; and in the case of **195** only the illustrated *endo* isomer is produced. The N,O bond of these adducts can be readily cleaved by hydrogenolysis over palladium catalysts to give C-3-branched-chain products. Levoglucosenone (**197**) is also an ideal substrate for 1,3-dipolar additions, and on reaction with benzonitrile oxide (**196**) it gives isoxazoline **198** as a single isomer in 71% yield. Again this indicates preferred *exo*-addition by attack at the less-hindered face of the dipolarophile.²¹¹

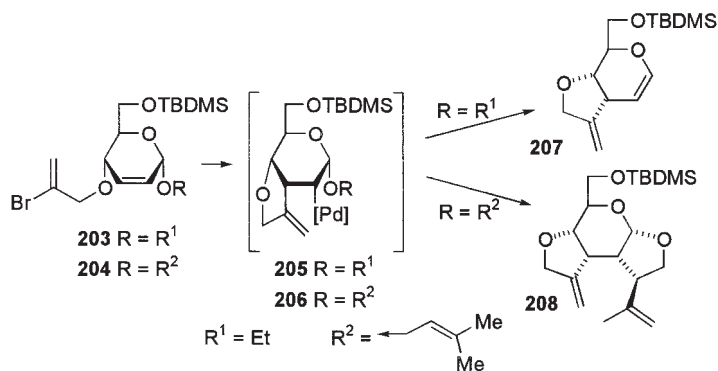


Cycloaddition reactions of unsaturated sugars with metal catalysts can give complex fused-ring products that in turn can act as precursors to a range of important noncarbohydrate compounds—notably natural products. They highlight the progress made in the application of synthetic methods developed in general organic and organometallic chemistry for use with carbohydrate derivatives. Trost's trimethylene methane complex **200**, made by ionization of 3-acetoxy-2-[(trimethylsilyl)methyl]-1-propene with catalytic tetrakis(triphenylphosphine)palladium(0),²¹² acts as a 1,3-dipole in adding to D-glucose-derived enone **199** to give adduct **201** in 70% yield when the reactants are used in the ratio 1.5:1. However, when the silylmethylpropene is employed in excess, the main product is a single diastereomer of *spiro*-cyclic **202** (Scheme 19). The reaction is believed to proceed via an initial Michael-like addition to the double bond,



SCHEME 19

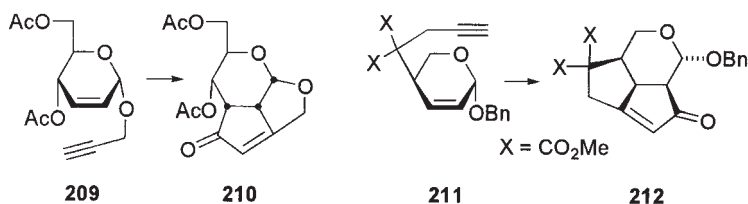
followed by an attack of the resulting C-3 anion on the η^3 -palladium complex. In most of these types of reactions, single isomers are obtained as a result of attack of the palladium complex on the less-hindered face of the pyranoside.²¹³



SCHEME 20

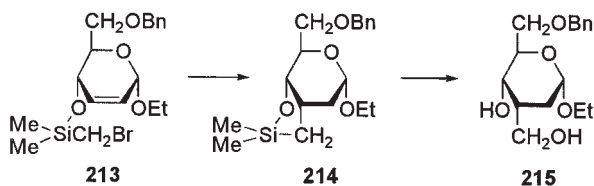
c. Intramolecular Cycloaddition Reactions.—The potency of metal-catalyzed cyclizations is perhaps best illustrated by the intramolecular Heck reactions shown in Scheme 20. In this example, the 2-bromoallyl ethers **203** and **204** are treated with palladium(II) acetate and triphenylphosphine to give the intermediates **205** and **206**, with the former undergoing Pd- β -alkoxy elimination to give **207** while the latter takes part in a further association-insertion reaction to give the tricyclic **208**. The efficiencies of both processes are about 70%.²¹⁴

A further addition-cyclization process that leads to complex fused-ring systems is the dicobalt octacarbonyl-mediated Pauson-Khand reaction which, applied to enynes **209** and **211**, gives respectively and in modest yields the tricyclic cyclopentenones **210**²¹⁵ and **212**.²¹⁶



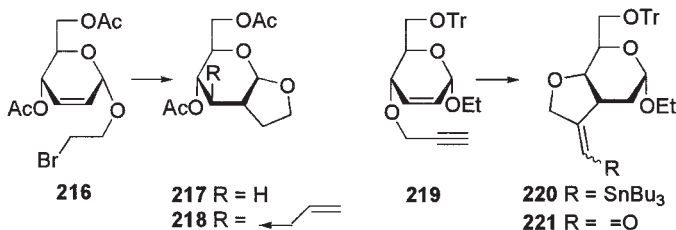
Radical cyclizations based on tin mediation present an additional method for effecting intramolecular additions to unsaturated sugar derivatives, the processes commonly occurring with both regio- and stereo-specificity.

A simple example involves the reaction of the silyl ether **213**, made from the corresponding 4-hydroxy-alkene by treatment with (bromomethyl)chlorodimethylsilane, with tributyltin hydride and a radical initiator. Bromine abstraction and intramolecular cyclization with the double bond leads to the bicyclic **214**, which upon oxidation with hydrogen peroxide gives the branched-chain **215** in an overall yield of 73% from the alcohol precursor of **213** (Scheme 21). When the sequence is conducted with the C-4 epimeric starting alcohol, the final product again has the hydroxymethyl group *cis*-related to the hydroxy group.²¹⁷

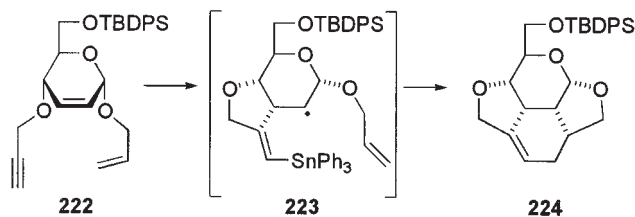


SCHEME 21

Reaction of the unsaturated bromoethyl glycoside **216** in the foregoing manner gives the bicyclic product **217**,²¹⁸ and similar treatment of the propargyl ether **219** with a tributyltin radical results in carbon-radical generation and cyclization to afford the tin-containing adduct **220** in 90% yield. On oxidation with osmium tetroxide and periodate ion, the Sn–C bond is cleaved, and the corresponding ketone **221** is produced in excellent yield.²¹⁹



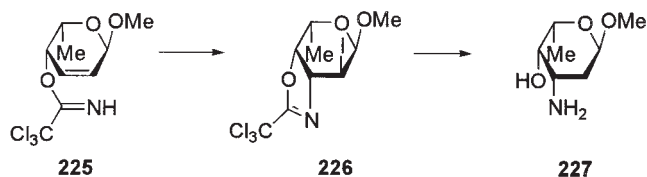
Adaptation of these cyclization reactions allows for the introduction of new C–C-bonded substituents so that, for example, when the bromoethyl glycoside **216** is activated with radicals generated with allyltributyltin (in place of the tributyltin hydride), the main product is the 3-C-allyl compound **218**. Otherwise, branching can be introduced by carrying out the radical-promoted reactions in the presence of radical-trapping species such as methyl acrylate.²¹⁸ With appropriate compounds, the initial organic radicals formed during intramolecular cyclization can be trapped by



SCHEME 22

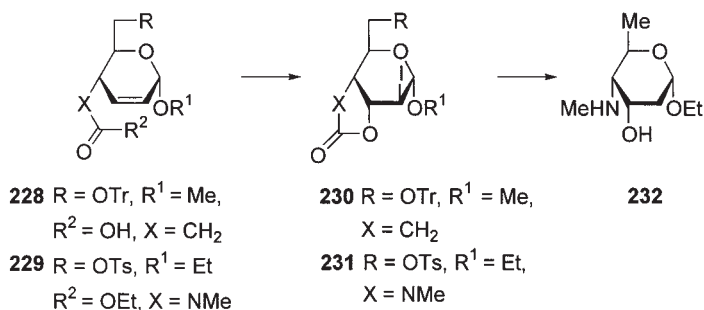
unsaturated functions within the same molecules, and in this way, for example, dienyne **222**, on reaction with triphenyltin hydride and triethylboron as radical initiator, gives compound **224** in 12% yield via radical **223** (Scheme 22). This intermediate can abstract a hydrogen atom directly from the tin reagent to give the main 2-deoxy reaction product (54%), or it can cyclize onto the double bond of the allyl group to give a new methylene radical that displaces a triphenyltin radical and gives the tetracyclic product **224**.²²⁰

Several ionic intramolecular cyclization reactions can be carried out on unsaturated compounds that have allylic substituents containing potential nucleophilic character, and this affords means of effecting specific additions to the double bonds. Iodonium dicollidine perchlorate provides electrophilic activation to the alkene group of allylic imidate **225** that consequently reacts to give the bicyclic iodooxazoline **226**, and, hence, by reductive dehalogenation with tributyltin hydride, followed by acid-catalyzed hydrolysis of the heterocyclic ring, the glycoside **227** of daunosamine (Scheme 23). Applied to the C-4 epimer of the starting material **225**, this strategy results in the glycoside of the amino sugar, ristosamine, which, relative to daunosamine, has inverted stereochemistry at C-3 and C-4.²²¹ A variation of the theme uses mercury(II) ion as an electrophile for the cyclization step with subsequent demercuration with sodium borohydride. This approach has been applied with the appropriate 2-C-methyl alkene to give access to the 3-amino-3-deoxy-3-C-methyl sugar required for the preparation of D-rubranitrose, which is a 3-deoxy-3-C-methyl-3-C-nitro analogue.²²²



SCHEME 23

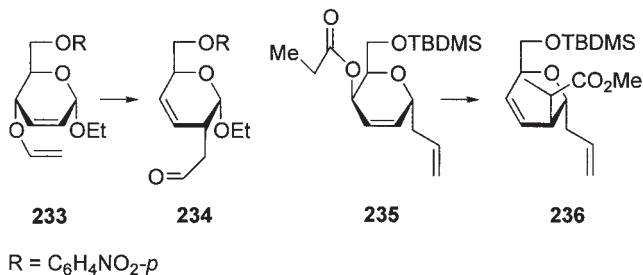
Similar reactions, again activated by iodonium species, involve the generation of lactone or oxazolidinone rings. For example, classical iodolactonization of the branched-chain sugar **228** affords the expected bicyclic product **230** stereoselectively and in high yield under mildly basic conditions with iodine–iodide.²²³ Otherwise, amino sugar derivative **229**, treated with iodonium dicollidine perchlorate, gives iodooxazolidinone **231**, which can be converted into the holacosamine derivative **232** (Scheme 24),²²⁴ this overall process being the complementary way (compare **225** → **227**) to introduce the *cis*-hydroxyamino functions into sugar rings from unsaturated starting materials.



Scheme 24

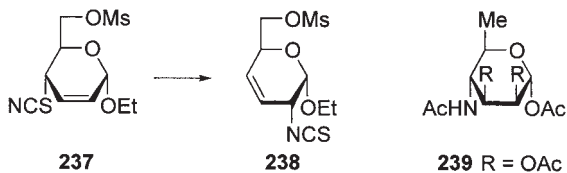
d. Rearrangement Reactions.—Many unsaturated sugar derivatives are ideally structured to take part in [3,3]-sigmatropic rearrangements, the most straightforward of which involve compounds with allylic ester groups. As already indicated the hydroxyglycal ester **128** rearranges on heating to the 2,3-unsaturated isomer **133** with stereochemical integrity. Such reactions are reversible, but in this case the equilibrium greatly favors **133** because of the dissimilarity of the double bonds of the isomers involved and their consequent free-energy difference. With 2,3-unsaturated 4-esters and their rearranged 3,4-unsaturated 2-esters isomers, no such difference exists, and thermal interconversions would be expected to result in mixtures. However, such conversions, do not occur readily²²⁵ and this approach is not of great value synthetically. Nevertheless, related processes, particularly those that are favored in the forward direction, are extremely useful. For example, Claisen rearrangement of vinyl ether **233**, which occurs on heating at 185 °C, gives the branched-chain aldehyde **234** in 75% yield,²²⁶ but difficulties in making the starting vinyl ethers efficiently limit this approach. The problem does not apply in the case of propanoate **235** which is converted into mixed epimers (at the chiral center in the branch, 7:1) **236** by conversion into the ketene silyl acetal, thermal rearrangement, desilylation, and methyl

esterification. This Claisen–Ireland rearrangement was used for work on synthetic studies of the diterpene forskolin which activates the enzyme adenylate cyclase.²²⁷ An alternative method for introducing branch chains applies the Meerwein–Eschenmoser amide acetal modification of the Claisen process. By this approach, a 3,4-unsaturated glycoside 2-ol has been converted to a 2,3-unsaturated product with an (*N,N*-dimethylcarboxamido)methyl substituent at C-4 for use in synthetic studies of thromboxanes.²²⁸

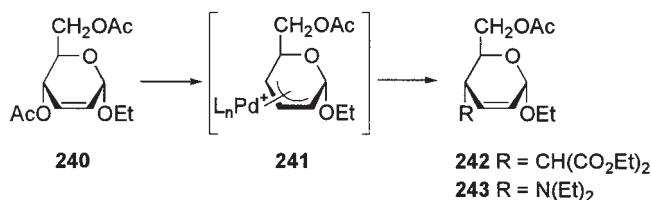


As already indicated, Claisen rearrangement of 2,3-unsaturated aryl glycosides can occur thermally to provide isomeric C-3 arylglycals, for example, (17 → 18).¹⁹

Related methods may be used to introduce amino functions. For example, thiocyanate **237**, made from the 4,6-dimesylate, rearranges to the isothiocyanate **238**,²²⁵ and 3,4-unsaturated 2-cyanates, easily made *in situ* from the corresponding carbamates, afford the *N*-bonded 4-isocyanates of the 2-enes.²²⁹ From both types of rearranged products aminodeoxy sugars may be accessed, and in this way perosamine peracetate (**239**) can be synthesized from the cyanate of a 3,4-unsaturated 2-ol, which is thermally rearranged prior to dihydroxylation and acetylation.²²⁹



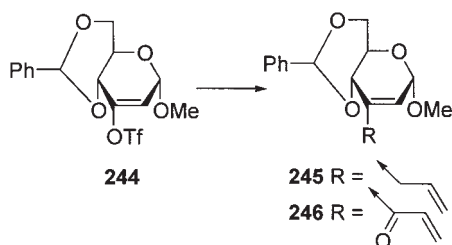
e. Displacements of Vinyl and Allyl Substituents.—Several metal-catalyzed reactions allow the displacement of allylic carboxylate and vinyl triflate groups on unsaturated sugars and thereby open new opportunities for functionalization. Of particular relevance is the Pd(0)-assisted displacement of the allylic ester functions by carbon and nitrogen nucleophiles.



SCHEME 25

For example diacetate **240**, treated with the anion of diethyl malonate, or with diethylamine, in the presence of triphenylphosphine and catalytic amounts of tetrakis(triphenylphosphine)palladium(0), gives the branched chain and amino compounds **242** and **243**, respectively, both in 80% yield, via the π -allyl Pd-complex **241** (Scheme 25; compare **145** \rightarrow **146**).²³⁰ Other studies have given indications that electronic factors have the major role in controlling the regioselectivity of such reactions and only in certain instances do subtle steric features play a role.²³¹

Vinylic triflates such as **244** also allow the introduction of C-bonded substituents: reaction with dilithium diallylcopper cyanide gives the 1,4-diene **245** in 76% yield,²³² and Stille coupling with tributylvinyltin and carbon monoxide in the presence of palladium(0) produces the dienone **246** in 71% yield.^{233,234}

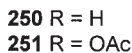


IV. OTHER ENOL ETHERS

1. Pyranoid 4-Enes and Furanoid 3-Enes (*endo*-Enes)

Compounds such as **247** (R = CH₂OH) are enol ethers closely related to the glycals (especially C-1 C-substituted glycals; Section II.3.a), but they differ significantly in retaining the acetal anomeric center. They are readily available from saturated hexopyranosides with unsubstituted hydroxyl groups at the primary positions and good leaving groups at C-4 simply by oxidation of the alcohol moieties to the aldehydes and spontaneous

An entirely different approach to pyranoid 4-enes depends on eliminations from 5-bromo compounds obtained from pyranoid hexuronic acid derivatives by photobromination. Treated with zinc–acetic acid, the bromide **249** gives the “glycal”-like **250** (62%), while the 4-acetoxy compound **251** is formed when DBU is used to promote elimination. Similarly, base treatment of penta-*O*-acetyl-5-bromo- β -D-glucose with DBU causes the analogous loss of hydrogen bromide and formation of the 4-acetoxy-4-ene, but use of zinc–acetic acid affords mainly the 5-*exo*-methylene alkene by the alternative available elimination process.²³⁷



The main chemical feature of the enol ethers covered in this section relates to the acid sensitivities of their glycosidic and enol ether groups. Consequently, the pyranoid and furanoid members hydrolyze readily in

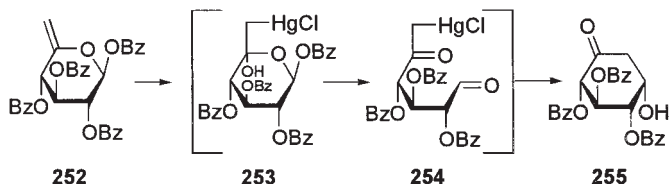
acid to give 4-deoxyaldos-5-ulose and 3-deoxyaldos-4-ulose derivatives, respectively.

2. Pyranoid 5-Enes and Furanoid 4-Enes (*exo*-Enes)

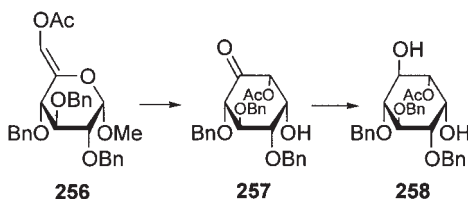
6-Deoxyhex-5-enopyranosyl compounds are usually prepared from hexopyranosides with leaving groups such as iodide, tosyloxy, or phenylselenoxy at the 6-position, while the 5-deoxy-4-enofuranosyl compounds are obtainable by eliminations from starting materials having leaving groups at C-5.²⁴⁰ Otherwise, 5-bromohexopyranose derivatives afford the pyranoid alkenes upon treatment with zinc–acetic acid.²³⁷

Pyranoid compounds such as **252** undergo hydroboration and hydrogenation to give mixtures of D-glucose and L-idose derivatives and their 6-deoxy analogues, respectively, the ratios depending on reaction conditions and on structural details of the substrates. Acid-catalyzed hydrolysis leads to 6-deoxyaldos-5-uloses.⁶

The main significance of hexopyranoid 6-deoxy-5-enes (such as **252**) is their considerable value in providing direct access to functionalized cyclohexane derivatives.^{204,241} Tetrabenzoate **252**, for example, on treatment with mercury(II) acetate (1.8 mol equiv.) in refluxing aqueous acetone containing acetic acid (1%) gives the hydroxycyclohexanone **255** after undergoing standard hydroxymercuration to **253**, which, as a hemiacetal, ring opens to give a product that loses benzoic acid from C-1 to afford the 6-deoxy-6-mercuri-aldos-5-ulose **254**. The doubly activated C-6 then promotes intramolecular aldol cyclization, and crystalline compound **255** is obtained in 93% yield (Scheme 26).²⁴² The reaction has frequently been applied in the synthesis of compounds related to the inositols, inosamines, and carba sugars (those having a methylene group instead of a ring oxygen atom). It mimics the key steps in the biosynthetic conversion of D-glucose 6-phosphate into *myo*-inositol 1-phosphate and in the production of shikimic acid and hence the benzenoid rings of the aromatic amino acids from 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate.^{204,241}



SCHEME 26



Scheme 27

A very significant development was introduced with the finding that 5-enes, which retain an oxygen-bonded substituent at C-6, take part in the rearrangement process. Thus, the enol acetate **256**, made from the 6-aldehyde by treatment with acetic anhydride and potassium carbonate, gives the inosose **257** in 57% yield on treatment with mercury(II) trifluoroacetate in aqueous acetone, and this ketone affords the specifically substituted *myo*-inositol **258** on reduction with sodium triacetoxyborohydride (Scheme 27).²⁴³ A significant route to inositols and specifically *O*-substituted derivatives is therefore available.

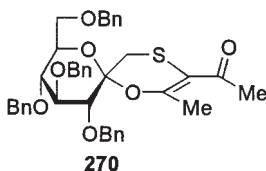
Other useful methods have been found to convert the 6-deoxy-5-enes into carbocyclic products while retaining the aglycons. For example, treatment of methyl glycoside **259** with triisobutylaluminum gives the deoxyinositol compound **260** in 79% yield by a route that leaves the C-1-OMe bond intact and causes stereospecific hydride transfer to reduce the carbonyl group. When applied to disaccharide derivatives with the double bond in the nonreducing moiety, cyclitol analogues with monosaccharide units replacing the methyl group of **260**, are obtained.²⁴⁴

Furanoid analogues such as **261**, made from the 5-deoxy-5-iodo- α -D-arabinofuranoside, do not give cyclopentane derivatives by mercury(II) promotion; instead 5-mercured-1,4-dicarbonyl compounds are formed and these do not cyclize.²⁴⁵

3. 2,6-Anhydroald-1-enitols (“*exo*-Glycals”)

Pyranoid members of this set are formally “2,6-anhydro-1-deoxyald-1-enitols,” compound **262** being representative. Having *exo*-methylene groups they resemble the pyranoid 5,6-enes and furanoid 4,5-enes of the last section, but they differ significantly in not having an acetal anomeric functional group. For obvious reasons they have been given the trivial name “*exo*-glycals.” Their synthesis is usually achieved from aldono-1,5-lactone derivatives by methylenation or by elimination procedures conducted on aldose derivatives containing both a one-carbon substituent and a leaving

from the β face of the double bond. Hydroboration of *exo*-alkene **262** affords the β -C-hydroxymethyl glucoside as a single product.²⁵³ As indications of how more complex C-glycosides can be derived, compound **262** can be converted into arylmethylene compounds (**264**) by reaction with arylmercury(II) acetates in the presence of palladium catalysts,²⁵³ and *spiro*-ketoside **270** and its anomer are formed simply by treatment of the same alkene with 3-thiophthalimide-2,4-pentanedione in the presence of pyridine.²⁵⁴ (See Scheme 6 for an analogous reaction of tri-*O*-benzyl-D-glucal.)

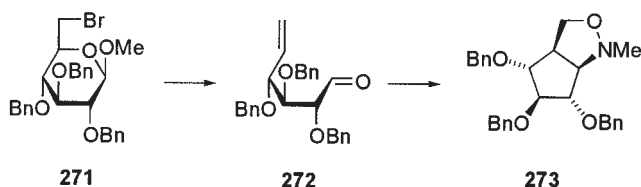


V. OTHER UNSATURATED DERIVATIVES

Acyclic carbohydrate derivatives containing unsaturation, with some exceptions, exhibit much of the chemistry already described for cyclic analogues, and their usefulness should not be overlooked. Unsaturated derivatives of alditols can be made, for example, by standard eliminations from alditol *vic*-disulfonates or epoxides or by β -eliminations from *O*-substituted 1-deoxy-1-nitroalditols and 1-deoxy-1-sulfonylalditols. Additions of hydrogen and ammonia to the unsaturated nitroalditols made in this way offer, respectively, routes to 2-deoxy- and 2-amino-2-deoxyaldoses.²⁵⁵

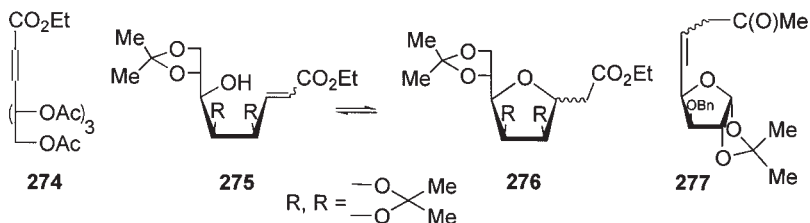
Of the several types of enals derivable from aldoses (see **80** and **81**), the 5,6-dideoxy-hex-5-enoses are of particular significance because of the efficient cyclization to give cyclopentane derivatives that they undergo on treatment with *N*-alkylhydroxylamines. The reactions are spontaneous and involve intramolecular 1,3-dipolar cycloadditions undergone by intermediate nitrones. For example, compound **272**, made by treatment of 6-bromo compound **271** with zinc in moist alcohol, on reaction with *N*-methylhydroxylamine gives the bicyclic product **273** in 80% yield (Scheme 28).²⁵⁶ This process gives simple access to many functionalized cyclopentanes.

An entirely different approach to unsaturated acyclic derivatives involves the generation of the multiple bonds by use of Wittig-like processes applied to aldehyde substrates with the oxidized carbon atom at either terminus of the carbon chain. Furthermore, the aldehydic moieties may be masked in



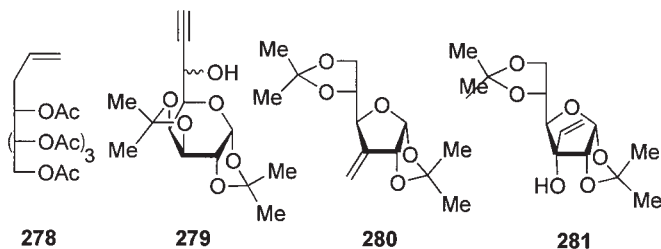
SCHEME 28

cyclic hemiacetal forms—as in free aldoses. By this means, for example, compounds **274**, **275**, and **277** may be efficiently produced. In the case of **275**, 2,3:5,6-di-*O*-isopropylidene-*D*-mannofuranose is the starting material, and the acyclic first product has the propensity to cyclize to the C-glycoside **276** as shown.²⁵⁷



Otherwise, unsaturation may be introduced by use of carbonyl-containing carbohydrate derivatives and carbon nucleophiles that contain alkene (or, if desired, alkyne) functionality, a notable illustration being the tin- or indium-mediated C-1 allylation of unprotected sugars. As an illustration, *D*-arabinose, treated with allyl bromide in aqueous ethanol in the presence of tin gives, after acetylation, **278** in 85% yield.²⁵⁸ In this procedure aldoses react better than do ketoses, and pentoses better than hexoses. More usual is the use of Grignard reactions to give, for example, the octynes **279**.

Very frequently, Wittig and Grignard reactions are applied to the relevant ketones to generate the branch points in compounds such as **280** and **281**.²⁵⁹



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CHEMISTRY OF ANHYDRO SUGARS

BY MILOSLAV ČERNÝ

Department of Organic Chemistry, Faculty of Science, Charles University,
Albertov 2030, 12840 Prague, Czech Republic

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I. INTRODUCTION

Anhydro sugars, also called intramolecular anhydrides (for historic and leading reviews, see Refs. 1–16) are heteromorphous sugar derivatives that formally arise by elimination of one or more water molecules from arbitrary hydroxyl groups of the parent aldose or ketose. They usually contain a bicyclic or tricyclic skeleton composed of oxirane, oxetane, oxolane (tetrahydrofuran), and oxane (tetrahydropyran) rings. If the hemiacetal group is involved in the formation of such a ring, the resulting glycoside anhydride (previously named “glycosan”) exhibits properties approaching ordinary glycosides—it is actually an intramolecular glycoside.

In general, the reactivity of anhydro sugars is determined mostly by the size of the oxygen rings. Oxirane and oxetane rings show a high reactivity, whereas oxolane and oxane rings are less reactive. However, the position of the anhydro bond, the steric arrangement, and the conformation of the molecule also play a significant role.

Nowadays, anhydro sugars constitute very versatile starting materials not only in carbohydrate chemistry but also for the synthesis of non-carbohydrate and nonnatural compounds. In the past two decades, interest in anhydro sugars has increased because they have been shown to be suitable monomers for preparing stereoregular polysaccharides and their specifically substituted derivatives.

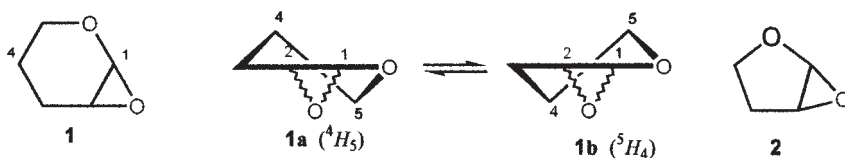
In this Chapter, only anhydrides of aldoses and ketoses are included. Anhydrides of acyclic carbohydrates, for example, alditols, aldonic acids, and intermolecular anhydrides are not discussed.

II. ANHYDRO SUGARS INVOLVING THE ANOMERIC CARBON ATOM IN THE ANHYDRO BOND

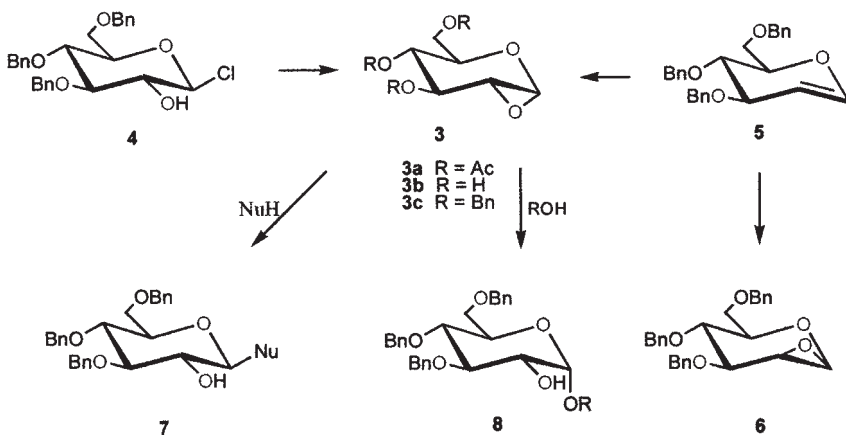
Compounds of this class, containing oxirane, oxetane, or oxolane rings are essentially internal glycosides derived from the pyranoid or furanoid form of aldoses and ketoses. They resemble conventional glycosides in undergoing acid hydrolysis in aqueous solutions to give reducing sugars. However, in contrast to ordinary glycosides, some of them, particularly those containing strained rings, also undergo hydrolysis in alkaline solution. The regioselectivity of opening of the anhydro ring is controlled by the intermediate formation of a carbocation at C-1, stabilized as the glycosyl oxocarbenium ion.¹⁷ Consequently, nucleophilic agents preferentially attack the anomeric carbon atom with formation of various glycosyl derivatives and/or glycosides, while the configuration at the corresponding nonanomeric carbon atom is retained. Many anhydro sugars behave as monomers in polymerization reactions, resulting in formation of stereoregular polysaccharides.

1. 1,2-Anhydroaldoses

1,2-Anhydroaldopyranoses have the 2,7-dioxabicyclo[4.1.0]heptane skeleton **1**, which preferentially adopts 4H_5 (**1a**) and 5H_4 (**1b**) conformations.^{18,19} 1,2-Anhydrohexofuranoses possess the more flexible 2,6-dioxabicyclo[3.1.0]hexane skeleton **2**, adopting an *E* conformation.



The first well-defined compound of this class is the extremely reactive 1,2-anhydro-3,4,6-tri-*O*-acetyl- α -D-glucopyranose (**3a**), referred to as “Brigl’s anhydride,” which can be prepared from β -D-glucopyranose pentaacetate by sequential treatment with PCl_5 and NH_3 ^{20,21} or by epoxidation of the corresponding entol.²² Anhydride **3a** was used in the synthesis of glycosides^{23,24} and α -D-linked disaccharides, in particular sucrose.²⁵ The unsubstituted 1,2-anhydro- β -D-glucopyranose (**3b**) has not been isolated, however, its intermediary existence is anticipated for some reactions,²⁶ such as the deamination of 2-amino-2-deoxy-D-mannose in ^{18}O water leading to labeled D-glucose,²⁷ or the treatment of phenyl β -D-glycopyranosides with aqueous alkalies or alkoxides, yielding 1,6-anhydro- β -D-glycopyranoses and corresponding β -D-glycopyranosides, respectively.^{28,29}



A series of perbenzylated 1,2-anhydro sugars of the following configurations has been described. 1,2-Anhydrohexopyranoses: *allo* and *altro*,³⁰ *gluco*,^{31–33} *manno*,³⁴ *galacto*,³⁵ *talo*,^{32,36}; 1,2-anhydro-6-deoxyhexopyranoses: *galacto*,³⁷ *manno*,³⁸ *gluco*,³⁹; 1,2-anhydropentopyranoses: *arabino*,⁴⁰ *xyl*o,¹⁹; 1,2-anhydrohexofuranoses: *gluco*,⁴¹ *manno*,⁴¹ *gulo*,⁴²; 1,2-anhydropentofuranoses: *arabino*,⁴² *lyxo*,⁴¹ *ribo*,^{43,44} *xyl*o.^{41,45}

In addition to benzyl ethers, various *O*-substituted 1,2-anhydro sugars have been described, for example pivaloyl,⁴⁶ *tert*-butyldimethylsilyl,^{33,47} 4,6-*O*-benzylidene,³³ and methyl.¹⁷ The anhydro sugars just mentioned have been prepared by several synthetic routes:

a. The partially benzylated (less often silylated or alkylated) aldose having a free OH group at C-2 is converted into the corresponding 1,2-*trans* glycosyl halide (mainly chloride,^{31,37,48,49} fluoride,^{35,37} or tosylate,²⁶ and then treated with an appropriate base (potassium *tert*-butoxide or sodium hydride), mostly in oxolane at room temperature to close the 1,2-oxirane ring. Thus, the benzylated β -D-glucopyranosyl chloride **4** yields 1,2-anhydro-3,4,6-tri-*O*-benzyl- α -D-glucopyranose (**3c**). This general procedure is the one most frequently used.

b. An alkylated 1,5-anhydro-1,2-dideoxy-glycos-1-enitol (such as **5**) is treated with various peroxy derivatives (*m*-chloroperoxybenzoic acid,^{40,50} hydrogen peroxide, dimethyl dioxirane,^{33,47,51} or oxaziridines²² to give, under very mild conditions in aprotic solvents, a single 1,2-anhydro sugar **3c** or a mixture of two stereoisomers (**5** \rightarrow **3c** and **6**).³⁴ However, this method may prove less convenient, particularly in cases when 1,2-anhydro sugars having a *cis* arrangement of the hydroxyl group at C-3 and oxirane ring are required.

c. Treatment with base of a partially protected aldose having a good leaving group at C-2, for example, a 2-*O*-tosyl or 2-bromo-2-deoxy group, affording the 1,2-anhydro sugar as a result of *trans*-cyclization.^{32,52}

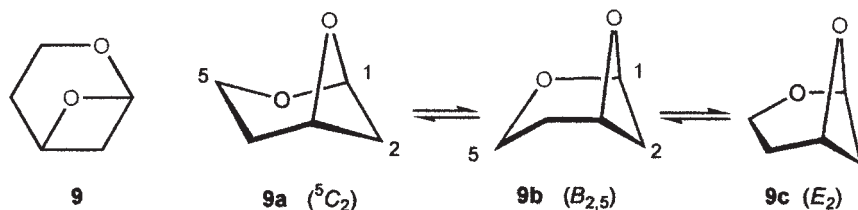
In comparison to the oxetane, oxolane, and dioxolane ring of other anhydro sugars, the reactivity of the oxirane ring in 1,2-anhydro sugars is markedly higher. Consequently, 1,2-anhydro sugars serve as stereoselective glycosylating agents.^{43,46,51,53,54} Starting with them, glycosides,^{46,48,51} disaccharides,^{37,38,51,55} thiocyanates,⁵⁶ glycosylamines,^{43,45} and C-glycosyl^{57–59} compounds can be prepared. As the configuration at C-2 of the anhydride bond is retained during the oxirane-ring opening reaction, both possible anomers may be formed, according to the reaction conditions and steric bulk of the nucleophile. Under mild conditions and at low temperature (S_N2 reaction conditions), small nucleophiles attack the oxirane ring to form *trans* products (**3** \rightarrow **7**), but under

forcing conditions (participation of the oxocarbenium-ion intermediate), at higher temperature, and with bulky and less-reactive nucleophiles, formation of *cis* products may be favored (**3** \rightarrow **8**). Lewis acids accelerate the glycosylation, but nevertheless, in some instances, glycosylation may be effected without added catalyst. For intramolecular glycosylations yielding 1,6-anhydrohexopyranoses, see Section II.4.

Polymerization of 1,2-anhydro sugars is a valuable method for preparing stereoregular (1 \rightarrow 2)-linked polysaccharides. As catalysts, Lewis acids such as PF₅ are generally used.^{60,61}

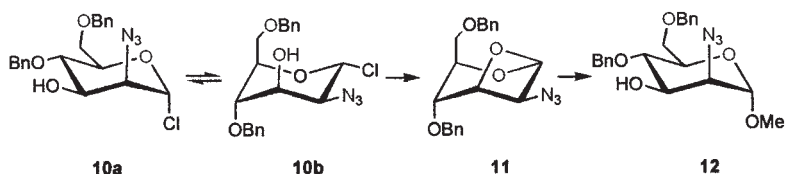
2. 1,3-Anhydroaldoses

These anhydro sugars have the 2,6-dioxabicyclo[3.1.1]heptane skeleton **9** and may adopt, for example, the ⁵C₂, B_{2,5}, or E₂ (**9a**–**9c**) conformations of the pyranose ring.⁶² The ⁵C₂ conformation **9a** is destabilized by axial substituents at C-2, C-4, and C-5.

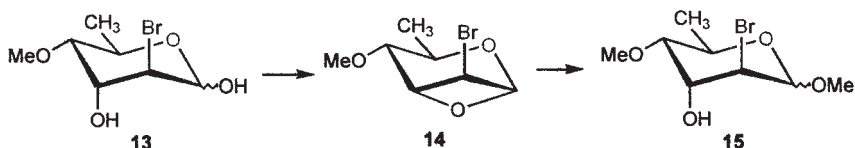


The oxetane ring of 1,3-anhydro sugars is quite reactive toward acids, even at room temperature,⁶² but in contrast to the oxirane ring of 1,2-anhydrohexoses the oxetane ring is relatively stable under basic conditions. Several 2,4,6-tri-*O*-benzyl-1,3-anhydrohexopyranoses of the following configurations have been prepared: *gluco*,^{63,64} *manno*,^{65,66} *galacto*,⁶⁷ *talo*,⁶⁸ and related 6-deoxy derivatives,^{62,66,69–72} respectively. A pentose example, 1,3-anhydro-2,4-di-*O*-benzyl- α -L-arabinopyranose is known.⁷³

All of the aforementioned compounds (except *altro*⁷¹) were obtained by the reaction of partially protected glycosyl chlorides with such strong bases as NaH or potassium *tert*-butoxide in oxolane (such as **10a** \rightarrow **10b** \rightarrow **11**). In some cases the ring-closure reaction is not sterically controlled by the α or β configuration of the intermediate glycosyl chloride.⁷³



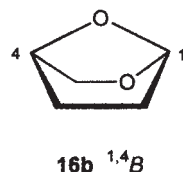
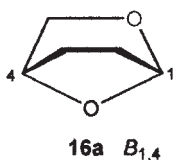
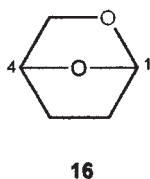
1,3-Anhydro-2,6-dideoxy-2-bromo-4-*O*-methyl- α -D-altropyranose (**14**) has been prepared from the corresponding α,β -D-altropyranose **13** under Mitsunobu reaction conditions.⁷¹ The glycosylation reaction of methanol with 1,3-anhydro-2-azido-4,6-di-*O*-benzyl- β -D-mannopyranose (**11**) in the presence of ZnCl_2 has been described as giving exclusively the methyl α -glycoside **12**⁷⁴ (see Ref. 73). In comparison, methanolysis of **14** proceeds at room temperature and results in formation⁷¹ of α - and β -glycosides **15**. Photolytic debromination of **14** with tributylstannane hydride does not disrupt the 1,3-anhydro bond.



Substituted 1,3-anhydroglucopyranoses undergo regioselective ring-opening polymerization reactions in the presence of acid catalysts to give (1 \rightarrow 3)- β -D-glucopyranans.^{75–77}

3. 1,4-Anhydroaldoses

These anhydro sugars have the general 2,7-dioxabicyclo[2.2.1]heptane skeleton **16** and should be named 1,4-anhydropyranoses (not 1,5-anhydrofuranoses).⁷⁸ They adopt only two rigid, non-interconvertible conformations $B_{1,4}$ and $^{1,4}B$ (**16a**, **16b**), respectively, which makes them markedly different from other anhydro sugars.



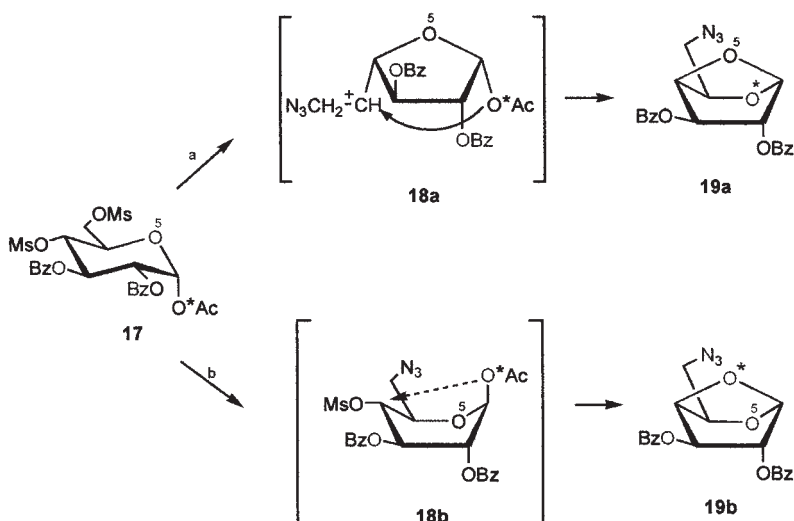
They are stable in basic solution, but are readily hydrolyzed with acids;⁷⁹ this is particularly true for 1,4-anhydro- β -D-galactopyranose, which decomposes on silica gel. 1,4-Anhydro-2,3-dideoxy- α -D-*glycero*-pentopyranose (**16a**) represents the basic skeleton of 1,4-anhydroaldoses in the $B_{1,4}$ conformation.⁸⁰

Compounds of this class have been prepared in the following configurations: D-*gluco*,⁸¹⁻⁸³ D-*galacto*,^{79,84} 6-deoxy-L-*manno*, L-*talo*,⁸⁵ L-*arabino*, D-*ribo*, D-*xylo*, and D-*lyxo*.⁸⁶⁻⁹⁰

Synthesis of 1,4-anhydro sugars can be effected by several methods:

a. By treatment with a strong base, such as NaH in oxolane, of partially protected (for example, benzylated) glycosyl halides having a free hydroxyl group at C-4 (compare Section II.2). The anomeric configuration of the leaving halogen is not necessarily dominant, both *trans*- and *cis*-ring closure are possible.^{81,83}

b. From the 4-*O*- or 5-*O*-sulfonylated (generally mesylated), partially protected pyranoses and furanoses, respectively, having a free hemiacetal group, by the action of a base^{85,89} (such as $\text{Me}_4\text{N}^+\text{OH}^-$) or sodium azide in DMF.⁸⁴ In the latter case, formation of the 1,4-anhydro bond takes place instead of displacement of the 4-sulfonyloxy group by azide ion.^{84,85} The mechanism of a similar displacement has been studied with 4,6-dimesylate **17** using ^{17}O NMR and an ^{18}O -induced isotope effect in the ^{13}C NMR spectra.⁹¹



Two pathways involving the replacement of the mesyloxy group at C-4 (**18a** and **18b**) and leading to 1,4-anhydrohexoses **19a** and **19b** were elucidated: (a) ring contraction by participation of the pyranose ring oxygen, (b) S_N2 intramolecular substitution of the mesyloxy group at C-4 by the O-1 oxygen atom. As could be anticipated, the mesyloxy group at C-6 was replaced by azide.

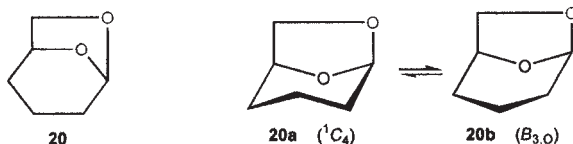
c. By vacuum pyrolysis of pentoses,⁸⁶ for example 1,4-anhydro-2,3-di-*O*-benzyl- α -D-ribopyranose, a useful monomer, was prepared by pyrolysis of D-ribose followed by benzylation.⁹² In contrast to other 1,4-anhydrohexoses, 1,4-anhydro- β -D-galactopyranose along with the corresponding 1,6-anhydropyranose and 1,6-anhydrofuranose are available in comparable yields (12–14%) by pyrolysis of D-galactose.⁷⁹

d. By isomerization of orthobenzoates or orthoacetates with HgBr₂ in acetonitrile⁹³ or by photochemical decarbonylation of isopropylidene derivatives of 1,6-anhydro- β -D-hexopyranos-2- and -4-uloses.⁹⁴

Special interest has been focused on ring-opening polymerization of 1,4-anhydroaldoses, which often proceeds with high stereoselectivity to afford stereoregular (1 \rightarrow 5)- α - or β -glycofuranans, mainly derived from pentoses,^{87,89,90,95–99} and (1 \rightarrow 4)-glycopyranans.^{92,100} Some ribofuranans show anti-AIDS virus activity.⁹⁷ Substituents on the monomer, as well as Lewis acid catalysis, play an important role in determining the stereoregularity of the resulting polymer.¹⁰¹ However, attempts to prepare stereoregular (1 \rightarrow 4)-D-glucopyranan by cationic polymerization of 1,4-anhydro-2,3,6-tri-*O*-benzyl- α -D-glucopyranose with various Lewis acids failed, thus indicating that the polymerization affords preferentially (1 \rightarrow 5)-D-glucofuranan.¹⁰² Some papers on copolymers exerting anti-AIDS virus activity have been published.^{103–107}

4. 1,6-Anhydroaldoses¹³

a. 1,6-Anhydroaldohexopyranoses.—The complete series of eight 1,6-anhydro- β -D-hexopyranoses (and of several enantiomers) has been described. These compounds have the 6,8-dioxabicyclo[3.2.1]octane skeleton **20** and are of limited steric flexibility, as represented by 1,6-anhydro-2,3,4-trideoxy- β -D-*glycero*-hexopyranose (**20a**).¹⁰⁸ Exclusively in the crystalline state,^{109–114} and generally in solution,^{115,116} they adopt the ¹C₄ chair conformation (**20a**). Nevertheless, some substituted 1,6-anhydrohexopyranoses exist in solution in a more or less flattened B_{3,O} conformation (**20b**). For correlation of their optical rotations with structure, see Ref. 108, 117–120.

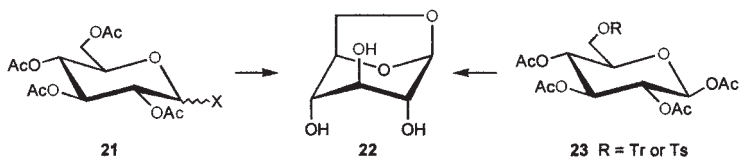


All stereocenters in 1,6-anhydrohexopyranoses are of inverted orientation compared to those in the parent ${}^4C_1(D)$ or ${}^1C_4(L)$ conformations of the corresponding hexopyranoses; for example, see **21**, **23**, and 1,6-anhydro- β -D-glucopyranose (**22**). In chemical properties, these compounds resemble to a certain degree the methyl β -D-hexopyranosides. They are relatively stable in alkaline media, but are readily hydrolyzed by acids. In aqueous acid solution, an equilibrium is established between the 1,6-anhydrohexopyranose and the corresponding aldohexose, whose composition correlates with expectations from conformational analysis and calculations from thermodynamic data.¹²¹ Extreme values, 0.2 and 86%, are observed respectively with 1,6-anhydro- β -D-glucopyranose (**22**) and 1,6-anhydro- β -D-idopyranose (the latter has all hydroxyl groups in equatorial disposition).

The following 1,6-anhydro- β -D-hexopyranoses have been described¹²²: *allo*,^{123–125} *altro*,^{126,127} *gluco*,¹²⁸ *manno*,^{110,129–131} *gulo*,¹³² *ido*,¹³³ *galacto*,¹³⁴ and *talo*.¹³⁵ Only a few of these are known in the L configuration, for example *ido*^{136a,b} or as racemates.¹³⁷

Various procedures have been used to obtain 1,6-anhydrohexopyranoses and their derivatives including acyl, alkyl, deoxy, azido, halo, and others:

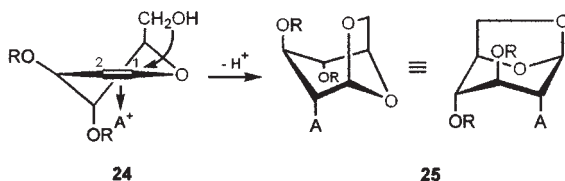
a. Cyclization of hexopyranosyl derivatives containing a good leaving group at C-1, preferably fluorides, bromides, azides,^{138–140} tosylates,²⁶ or 2,4,6-trimethylbenzoates,¹⁴¹ and various alkali-sensitive glycosides, for example phenyl glycosides^{142,143} by the action of strong bases (**21** \rightarrow **22**). The cyclization of unsubstituted phenyl glycosides can be performed with both anomers at elevated temperature to afford 1,6-anhydro- β -D-glucopyranose.¹⁴⁴ However, analogous cyclizations of aryl glycosides substituted in the phenyl group by electron-withdrawing groups, as with pentachlorophenyl¹⁴⁵ or pentabromophenyl glycosides, proceed under mild conditions by the action of tetrabutylammonium hydroxide, and their scope is greater.^{146,147} In all of these cyclizations the hydroxyl group at C-6 is usually free or is protected by groups readily removable under basic reaction conditions.



b. Cyclization of 6-*O*-tritylated^{128,148} or 6-*O*-benzylated^{149,150} hexopyranose 1-acetates (**23** → **22**) effected by activation of the anomeric group with SnCl₄ or TiCl₄ (and other Lewis acids¹²⁸).

c. Cyclization by base of 6-*O*-tosyl hexopyranoses (glucose **23** and mannose) having a free or acetylated anomeric hydroxyl group;^{130,151–153} however, this method fails, surprisingly, with galactose.¹²⁹

d. Cyclization of 1,5-anhydro-2-deoxy-hex-1-enitols (previously named glycals) by the action of Lewis acids or cationic agents in aprotic solvents.^{154–158} Attacking agents enter at C-2 of the starting hex-1-enitols to give 2-substituted 1,6-anhydrohexopyranoses (**24** → **25**).

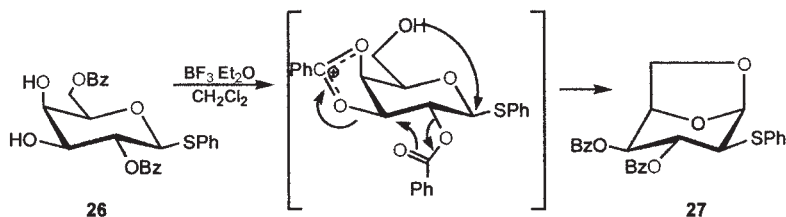


e. Treatment of a free hexose in solution with acids, resulting in the formation of an equilibrium mixture containing both the starting free hexose, the corresponding 1,6-anhydrohexopyranose, and usually 1,6-anhydrofuranose as a minor product.¹²¹ Similar cyclizations also proceed with hexose derivatives such as 2-, 3- or 4-*O*-alkyl, C-alkyl, deoxy, esters, acetals, and glycosides.^{159–163} 1,6-Anhydrohexoses may appear as artifacts¹⁶⁴ under hydrolytic conditions used with some natural compounds, particularly those containing altrose, gulose, idose, and their derivatives.

f. Pyrolysis of cellulose and starch, oligosaccharides, and hexoses.¹⁶⁵ The pyrolysis of cellulose is practical for large-scale preparations of 1,6-anhydro- β -D-glucopyranose (levoglucosan) on an industrial scale. It is essentially a thermal depolymerization, which has been studied in detail.¹⁶⁶ Typical yields vary around 20–35% and are dependent on the crystallinity of the polysaccharides, the presence of impurities (inorganic cations), pretreatment with acids, the temperature, pressure, and the construction of the reactor. Small amounts of an acid salt may markedly improve the yield, whereas the presence of alkali metal cations has the opposite effect. The high-temperature pyrolysis of acid-loaded cellulose produces mainly 1,6-anhydro-3,4-dideoxy-D-glycero-hex-3-enopyranos-2-ulose (levoglucosenone).^{3a} It is remarkable that the pyrolysis of cellulose in the presence of Cu powder produces small amounts of 1,6-anhydro- β -D-allose and - β -D-altrose.¹⁶⁷ As a model compound for the pyrolysis of cellulose, cellobiitol has been studied; a 32% yield of levoglucosan (**22**) was achieved.¹⁶⁸

g. Total synthesis starting from dimerization of acrolein, and resulting in racemates.^{169,170}

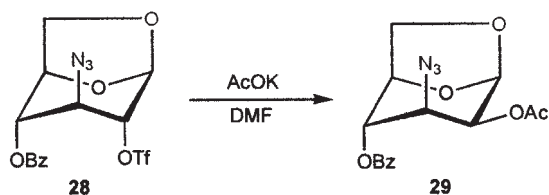
h. Miscellaneous methods. Cyclization of 2,3-dideoxy-hex-2-enopyranosides with hydrogen halides to give 1,6-anhydro-2,3-dideoxy-3-halo-hexopyranoses.¹⁷¹ Treatment of the orthoacetate prepared from benzylated L-gulose acetate with SnCl_4 to form 1,6-anhydro-2,3-di-*O*-benzyl- β -L-gulopyranose¹⁵⁰ (compare Ref. 172). One-pot condensation of hydroxyl groups at C-1 and C-6 of the corresponding hexopyranoses with *N,N'*-sulfuryldiimidazole and sodium hydride.¹⁷³ Cyclization of a 6-*O*-(octyloxy) dimethylsilylated phenyl 2,3,4-tri-*O*-benzyl-1-thio- α -D-glucopyranoside with *N*-iodosuccinimide to afford tribenzyl levoglucosan.¹⁷⁴ In contrast, phenyl 2,6-di-*O*-benzoyl-1-thio- β -D-galactopyranoside (**26**), having a participating benzoyl group at C-2, gives 1,6-anhydro-3,4-di-*O*-benzoyl-2-*S*-phenyl-2-thio- β -D-idopyranose (**27**) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and pyruvate via a benzoyl and phenylthio migration sequence.¹⁷⁵ For inversion of the configuration of a secondary hydroxyl group in 1,6-anhydrohexopyranoses by nucleophilic replacement or by an oxidation–reduction reaction (see p. 134).



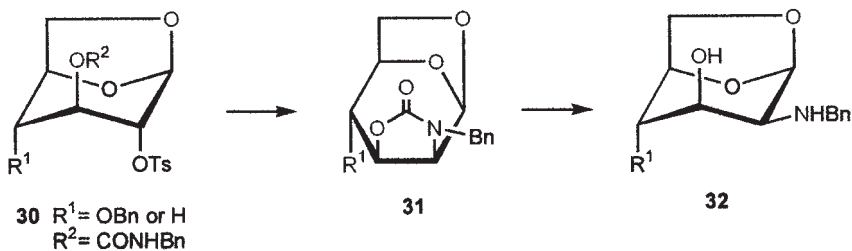
(i) *Reactions of 1,6-Anhydrohexopyranoses.*¹³—Individual hydroxyl groups in 1,6-anhydrohexopyranoses may differ in their steric orientation, and consequently, in reactivity. When the hydroxyl group at C-3 adopts the axial disposition, it is sterically hindered and is less reactive than other axial groups in the molecule. This permits preferential modification (tosylation, benzylation, oxidation, and so on) of the remaining axial or equatorial hydroxyl groups at C-2 and C-4,^{176,177} but equatorial hydroxyl groups are generally—with few exceptions^{135,178}—more reactive than the axial ones. Several enzymes have also been used to achieve selective acylation or oxidation.¹⁷⁹ An efficient selective *O*-debenzylation has also been described.¹⁸⁰

Sulfonyloxy groups may undergo bimolecular replacement reactions with nucleophiles, either external or internal, according to their axial or equatorial disposition and/or potential neighboring-group participation.

Axial and equatorial sulfonyloxy groups at C-4 can be replaced with inversion of configuration,^{181–183} whereas axial sulfonyloxy groups on C-2 resist such substitution, apparently because of unfavorable interactions of the approaching nucleophile with the O-6 oxygen atom of the 1,6-anhydro bond. However, under forcing conditions, in the presence of the nonparticipating azido group axial at C-3, displacement of the axial trifluoromethanesulfonyloxy group at C-2 with potassium acetate was successful (**28** → **29**).¹⁸⁴ (On the other hand, attempted displacement of the axial sulfonyloxy group on C-2 involved participation of O-6 and gave a 2,6-anhydrohexose derivative.^{185,186})

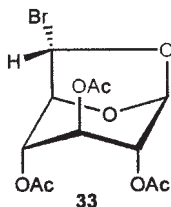


In the presence of a participating group at C-3, internal substitution proceeds without difficulty,^{187,188} see **30** → **31** → **32**.

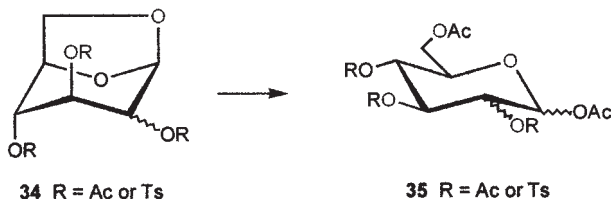


An axial sulfonyloxy group at C-3 can be displaced by external nucleophiles with inversion of configuration, provided that no axial and nonparticipating substituent is present at C-2 and/or C-4.¹⁸⁹ Interestingly, the equatorial trifluoromethanesulfonyloxy group on C-2 is reactive enough to be replaced with inversion by azide^{130,190a,b} or fluoride ion.^{190c} The cyclic sulfates from benzylated 1,6-anhydro- β -D-mannose and D-galactose yielded mainly the *trans*-diaxial products, whereas the corresponding cyclic 2,3-sulfate of 1,6-anhydro- β -D-talopyranose gave the *trans*-diequatorial product.¹⁹¹ 1,6-Anhydrohexopyranose triacetates (or benzoates), when treated with strong acids, yield equilibrium mixtures of isomers.^{162,192–194} Their radical bromination may be effected with

high regio- and stereoselectivity at C-6, to form C-6-*exo* bromo compounds,¹⁹⁵⁻¹⁹⁷ for example **33**. Irradiation of 1,6-anhydro-3-deoxy-3-*C*-succinimido- or 3-*C*-glutarimido- β -D-glucopyranose at 254 nm gave azepanedione and azocanedione derivatives, respectively.¹⁹⁸



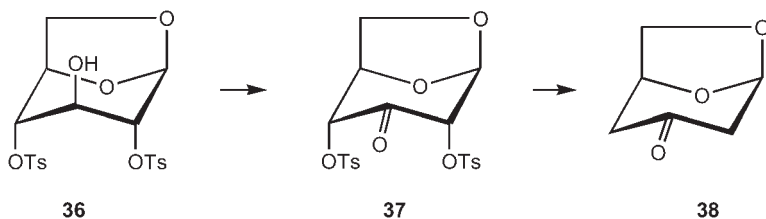
Hydroxyl groups in partially substituted compounds may be transformed into halo, amino, oxo, deoxy, and other functional groups. Free 1,6-anhydrohexopyranoses^{199,200} and their aminodeoxy^{201,202} derivatives tend to form cationic and anionic complexes, in particular with 1,6-anhydro- β -D-allopyranose, which has a vicinal triol system in axial-equatorial-axial arrangement.²⁰⁰



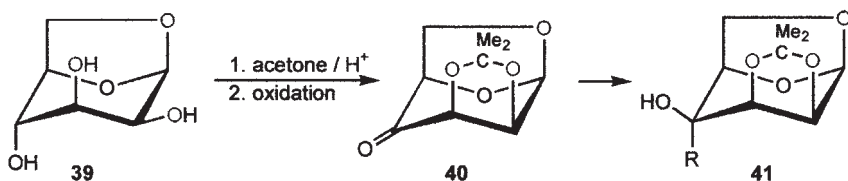
The final step for many transformations of 1,6-anhydrohexoses is the cleavage of the 1,6-anhydro bond by hydrolysis, acetolysis, thioacetolysis, halogenolysis, alcoholysis, and the like. Acetolysis (**34** \rightarrow **35**) with acetic anhydride (catalyzed by trifluoroacetic acid,²⁰³ triethylsilyl trifluoromethanesulfonate, or scandium triflate²⁰⁴) followed by deacetylation by the Zemplén method is relatively mild, and is the method most often used for obtaining the corresponding reducing saccharides. In these reactions, electron-withdrawing substituents at C-2 enhance the stability of the acetal group toward acids, whereas replacement of a hydroxyl group by hydrogen diminishes it. The 1,6-anhydro bond is generally cleaved more readily than a normal α - or β -glycosidic bond, and this may be conveniently exploited in preparing various oligosaccharides via glycosylated 1,6-anhydrohexopyranoses.²⁰³ Hydrogen bromide in acetic acid affords the corresponding glycopyranosyl bromide¹³ or even its 6-bromo-6-deoxy derivative.²⁰⁵

The most important and readily available compound among 1,6-anhydrohexoses is 1,6-anhydro- β -D-glucopyranose (levoglucosan, **22**). This compound is a valuable starting material for the preparation of various sugar derivatives, as well as natural and nonnatural compounds of biological importance;³ for biochemical studies, see Refs. 206, 207. Among the various preparative methods, thermolysis of cellulose and starch is the procedure of choice for large-scale preparation of levoglucosan.^{165,166,208} Molecular mechanics calculations and NMR data show²⁰⁹ that the unsubstituted levoglucosan adopts the 1C_4 conformation, but bulky and polar substituents at C-2 and C-4 force the chair conformation to flatten and/or to invert into the $B_{3,0}$ boat conformation. A similar situation is induced by the presence of an ammonium group at C-3.²⁰⁹

A key compound for levoglucosan chemistry is 1,6-anhydro-2,4-di-*O*-tosyl- β -D-glucopyranose (**36**)¹⁷⁶ which, after treatment with sodium ethoxide, affords a valuable starting compound, 1,6:3,4-dianhydro-2-*O*-tosyl- β -D-galactopyranose, as a single product (see Section IV.1). Another example illustrating synthetic versatility of the ditosylate **36** is its oxidation to 3-keto derivative **37**^{124,210,211} followed by reductive detosylation to afford the useful chiral synthon, 1,6-anhydro-2,4-dideoxy- β -D-glycero-hexopyranos-3-ulose (**38**).^{210,212} Keto derivative **37** is readily isomerized by the action of pyridine into compounds of the *D*-arabino, *D*-xylo, and *D*-lyxo configurations.²¹⁰

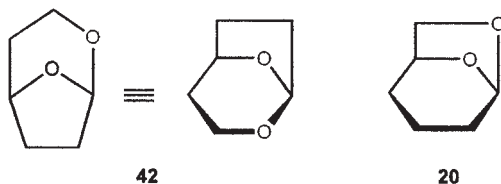


Other versatile compounds include 1,6-anhydro- β -D-mannopyranose (**39**) and 1,6-anhydro- β -D-galactopyranose,^{213,214} which can be converted into 2,3-*O*- and 3,4-*O*-isopropylidene derivatives, respectively. Compound **39** can be isopropylidenated and then oxidized to give ketone **40**. Reduction of **40** or its reaction with organometallic reagents affords derivatives (**41**) of 1,6-anhydro- β -D-talopyranose because of favored approach of nucleophilic reagents to the carbonyl group from the nonhindered *exo* side. Mild acid hydrolysis removes the isopropylidene group without cleavage of the 1,6-anhydride bond.²¹⁵ A similar reaction sequence has been applied to 1,6-anhydro- β -D-galactopyranose.



Polymerization and copolymerization of 1,6-anhydrohexopyranoses is of particular interest with regard to preparation of highly stereoregular polysaccharides of prospective practical utility.^{14,15} Various ethers, particularly benzyl, allyl, and silyl ethers of 1,6-anhydrohexoses are generally used as monomers. Protecting groups may control the anomeric specificity in formation of the α - or β -glycosidic bond. Thus, linear α -(1 \rightarrow 6)-D-glucopyranan (dextran)²¹⁶⁻²¹⁹ and its 2-amino-2-deoxy-,²²⁰ 3-azido-3-deoxy-,²²¹ 3-fluoro-3-deoxy-²²² derivatives, α -(1 \rightarrow 6)-D-galactopyranan,^{223,224} -D-mannopyranan,^{223,225,226} -D-allopyranan,^{227,228} and 3,4-dideoxyhexopyranan²²⁹ have been described. Synthesis of a stereoregular α -(1 \rightarrow 3)-branched α -(1 \rightarrow 6)-D-glucopyranan from silylated 2,4-di-*O*-benzyl levoglucosan is the first example of this kind,²¹⁷ and several copolymers^{230,231} have also been described.

b. 1,6-Anhydroaldofuranoses.—A complete series of eight 1,6-anhydroaldohexofuranoses has been described:²³² β -D-*allo*,²³³ β -L-*altro*,²³⁴ α -D-*galacto*,^{79,235} β -D-*gluco*,²³⁶ α -L-*gulo*,²³⁷ α -L-*ido*,²³⁸ β -D-*manno*,²³⁷ and α -D-*talo*.²³⁹ The basic skeleton of this class of compounds is 2,8-dioxabicyclo[3.2.1]octane (**42**) which is sterically similar to the 6,8-dioxabicyclo[3.2.1]octane skeleton **20** of 1,6-anhydrohexopyranoses.



Both of these classes of compounds differ only in the location of the oxygen atoms and display similar properties. They are stable in alkaline solutions, but are hydrolyzed in acids at approximately the same rate. Nevertheless, this hydrolysis is slower than with ordinary alkyl hexofuranosides. An equilibrium is established between free hexoses and their anhydro derivatives in aqueous acid solution, which in general contains only minor proportions (about 1–3%) of 1,6-anhydrofuranoses

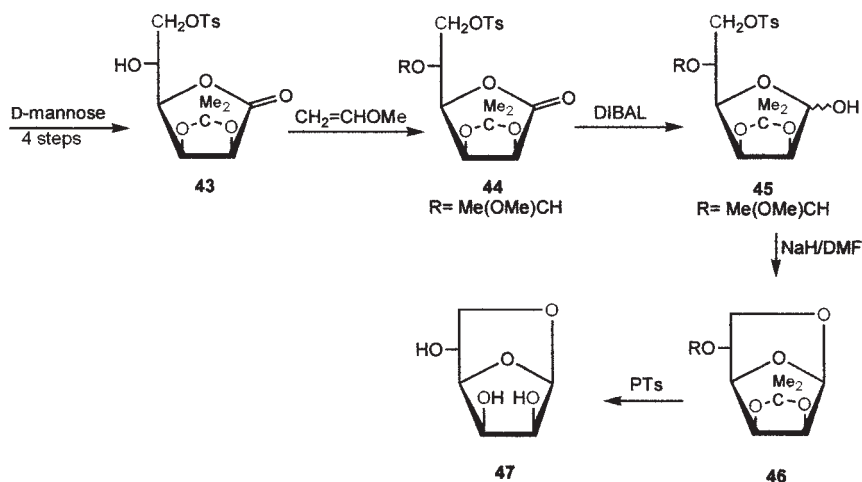
as compared to 1,6-anhydropyranoses (1–76%).²⁴⁰ This may be ascribed to the decreased stability of 1,6-anhydrofuranoses caused by different steric repulsions of the hydroxyl groups attached to the oxolane and 1,3-dioxane ring. A simple relationship exist between the structure and optical rotation of 1,6-anhydrohexofuranoses.^{233,239}

1,6-Anhydrohexofuranoses may be prepared by the following methods:

a. Treatment of free sugars in *N,N*-dimethylformamide solution in the presence of *p*-toluenesulfonic acid.²⁴¹ Under these conditions, the furanose:pyranose ratio in the reaction mixture is much higher than in aqueous acid solution, and the yields of furanoses range up to 33% for the *galacto*, *allo*, and *talo* isomers. An analogous method is based on cyclization under Lewis acid catalysis of alkyl furanosides that are protected at position C-5 in order to prevent the formation of the 1,4-anhydro bond.^{238,242}

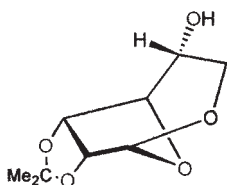
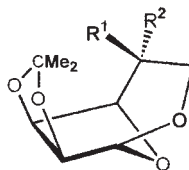
b. Vacuum pyrolysis of hexoses, oligosaccharides, and some polysaccharides, which yields small amounts of furanoses as side products alongside the pyranoses. In case of D-galactose, the yields of both pyranose and furanose 1,6-anhydrides are approximately 14%.⁷⁹

c. Cyclization of a protected 6-tosylate of D-mannofuranose to give the otherwise less accessible 1,6-anhydromannofuranose, as illustrated in the sequence 43–47.¹⁶⁴



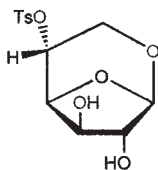
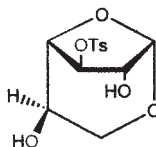
d. Hydroxylation of a double bond in 1,6-anhydro-2,3-dideoxy-hex-2-enofuranoses.²⁴³

O-Isopropylidene derivatives of 1,6-anhydrofuranoses are formed by reaction of their *cis*-diol group with acetone^{192,233,237} (see also Ref. 244). Among these, the *D-allo* derivative **48** is more stable toward acid hydrolysis than the *L-gulo* **49a** and *D-manno* **49b** isomers, which undergo deprotection with extreme ease under mild acid conditions owing to steric compression between the *endo*-dioxolane ring and the more stable 1,6-anhydro bond.

**48** *D-allo*

49a *L-gulo* $R^1 = \text{OH}, R^2 = \text{H}$
49b *D-manno* $R^1 = \text{H}, R^2 = \text{OH}$

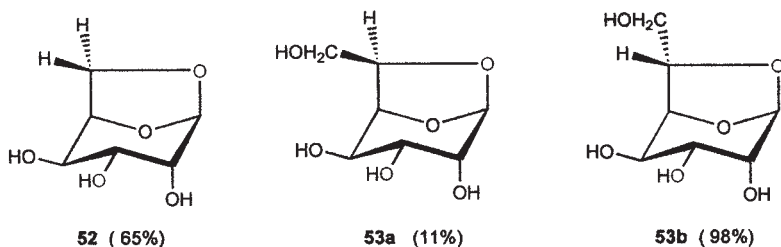
(i) *Reactions of 1,6-Anhydrohexofuranoses.*—The *exo*-oriented hydroxyl groups at C-2 and C-3 of the oxolane ring show increased reactivity as compared to that of the *endo* hydroxyl groups, as may be deduced from inspection of molecular models. The same is true for the axial *exo*-oriented hydroxyl group at C-5. This is illustrated by selective tosylation of 1,6-anhydro- β -D-glucofuranose, which gives the 5-tosylate **50**.²⁴⁵ On the other hand, selective tosylation of 1,6-anhydro- α -D-galactofuranose, which has an *endo*-hydroxyl group at C-5, gives mainly the 3-tosylate **51**²⁴⁶ (for selective oxidation at C-5, see Ref. 234).

**50****51**

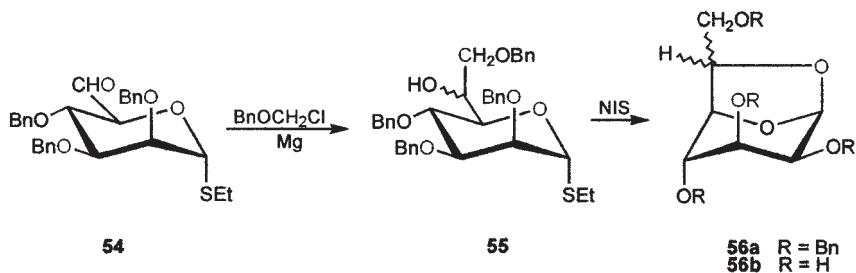
5. 1,6-Anhydro Derivatives of Aldoheptoses and Higher Aldoses

The basic skeleton of these anhydrides, 1,6-dioxabicyclo[3.2.1]octane, is identical to that of 1,6-anhydrohexopyranoses (see Section II.4). For the 32 diastereoisomeric Aldoheptoses, three different types of anhydrides may be formed in acid solution: 1,6-anhydrofuranoses, 1,6-anhydrofuranoses,

and 1,7-anhydropyranoses (see Section II.6). The composition of equilibrium mixtures thus obtained depends on the heptose configuration and can be predicted from conformational analysis.^{247,248} For example, when the hydroxymethyl group at C-6 is in the *exo* position, the proportion of the anhydrohexopyranose is markedly higher than in the case when it is oriented *endo*. Thus, the contents of 1,6-anhydro- β -D-gulopyranose (**52**), 1,6-anhydro-D-*glycero*- β -D-gulo-heptopyranose (**53a**), and 1,6-anhydro-L-*glycero*- β -D-gulo-heptopyranose (**53b**) in the equilibrium mixture with the parent sugars are 65, 11, and 98%, respectively. This example also suggests that a secondary hydroxyl group shows higher tendency to form the anhydro bond than a primary hydroxyl group.



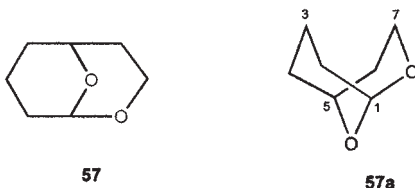
The following 1,6-anhydroheptopyranoses and their tosylates were prepared by conventional methods in the D-*glycero* series: β -D-gulo^{249,250} and β -D-ido.²⁵¹ An alternative method was developed for the synthesis of 1,6-anhydro-L- and -D-*glycero*- β -D-manno-heptopyranose (**56**) starting from the modified ethyl 1-thio- α -D-mannoside **54** via intermediate **55**²⁵² using *N*-iodosuccinimide to effect cyclization.



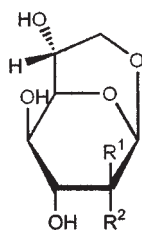
A multistep synthesis of a branched-chain 1,6-anhydro-D-*glycero*-D-*gluco*-heptofuranose²⁵³ from D-glucose has been reported. 1,6-Anhydro-2,3-dideoxy-3(*S*)-D-*glycero*-L-*gluco*- and -L-*manno*-nonopyranose have been described.²⁵⁴

6. 1,7-Anhydroheptoses

The basic skeleton of these compounds is 2,9-dioxabicyclo[3.3.1]nonane (**57**), which has limited steric flexibility. 1,7-Anhydroheptoses adopt predominantly the twin-chair conformation **57a**, provided that no *endo* substituents are present at positions C-3 and C-7 to cause steric interactions. Otherwise, flattened boat-like and skew conformations may also play an important role.²⁴⁷



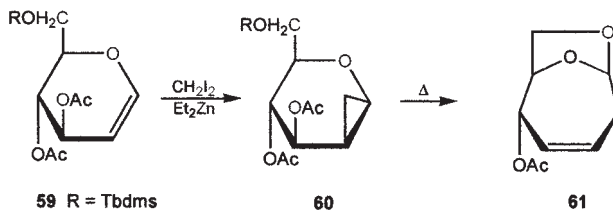
Only two 1,7-anhydrohexopyranoses have been described thus far: 1,7-anhydro-D-glycero- β -D-gulo-heptopyranose (**58a**)^{247,250} and the corresponding D-ido isomer (**58b**).²⁴⁷ They appear in the reaction mixture with 1,6-anhydro derivatives after acid treatment of solutions of the parent aldoheptoses.



58a D-glycero-D-gulo $R^1=H$, $R^2=OH$

58b D-glycero-D-ido $R^1=OH$, $R^2=H$

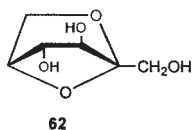
An unusual oxepane derivative, 5-O-acetyl-1,7-anhydro-2,3,4-trideoxy- β -D-erythro-hept-3-enoseptanose (**61**) was obtained by methylenation of the double bond in **59** and subsequent ring expansion of the intermediate **60**.²⁵⁵



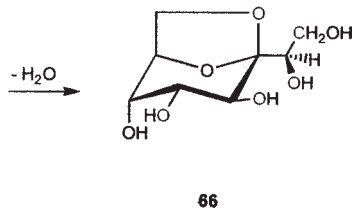
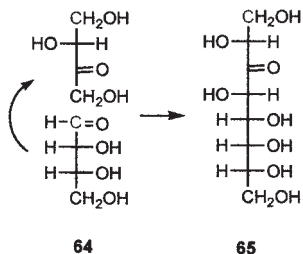
7. Anhydroketoses

Most compounds of this class are derived from 2-ketoses and exhibit properties related to the anhydroaldoses previously discussed. Among them, 2,7-anhydrohept-2-uloses, possessing the 6,8-dioxabicyclo[3.2.1]heptane skeleton (compare 1,6-anhydrohexopyranoses) are those the longest known and most intensively studied (see Ref. 1, p. 433), for example 2,7-anhydro- β -D-*altro*-hept-2-ulopyranose (sedoheptulosan),²⁵⁶ - β -L-*galacto*-hept-2-ulopyranose, - α -L-*galacto*-hept-2-ulofuranose,²⁵⁷ and - β -D-*talo*-hept-2-ulopyranose.²⁵⁸ They were prepared by equilibration of heptuloses in aqueous acid solution,²⁵⁷ by heating of phenyl glycosides in alkaline solution,²⁵⁹ or by an oxidation-reduction sequence from sedoheptulosan.²⁵⁸ Their tosylation, condensation with acetone, and transformation to 4-amino-4-deoxy derivatives has been described.²⁶⁰

Several anhydro derivatives has been isolated from the tars resulting from pyrolysis of parent ketohexoses (or ketohexose-containing saccharides): 2,5-anhydro- α -D-fructopyranose (**62**),²⁶¹⁻²⁶⁴ - α -D-tagatopyranose,²⁶¹ - α -D-psicopyranose,^{94,261} and - α -L-sorbiopyranose²⁶¹ (These compounds were previously named as 2,6-anhydrofuranoses, see Ref. 78.)



Benzylated 1,2-anhydro- β -D-fructopyranose (**63**) has been prepared from 1,2-*O*-isopropylidene- β -D-fructopyranose via the 1-*O*-tosyl- or 1-deoxy-1-iodo derivatives.²⁶⁵ Related 1,2-anhydro- α - and β -D-fructofuranose and 1,2-anhydro-3,4,5,7-tetra-*O*-benzyl-D-*gluco*-hept-2-uloses were obtained by epoxidation of unsaturated compounds. Benzylated anhydrides are especially acid labile and decompose during chromatography, but can be used as glycosylating agents.²⁶⁶ Predictably, benzoyleated 1,2-anhydrides are much more stable. The D-*glycero*-D-*manno*-oct-3-ulose (**65**) and the corresponding 3,8-anhydro derivative (**66**) were obtained by the self-aldol reaction of D-erythrose **64**.²⁶⁷



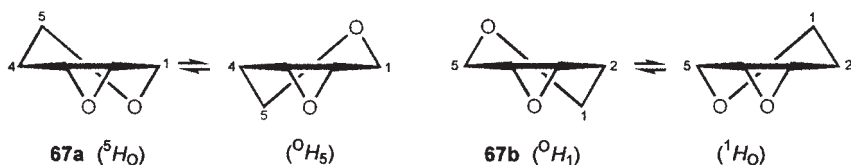
Acid treatment of the carboxyl-reduced derivative of *N*-acetylneuraminic acid yields the 2,7-anhydride of the corresponding non-2-ulopyranose.²⁶⁸

III. ANHYDRO SUGARS NOT INVOLVING THE ANOMERIC CARBON ATOM IN THE ANHYDRO BOND

1. Endocyclic Oxirane Derivatives (Epoxy Sugars)



Anhydro sugars of this type, having an oxirane ring fused with a pyranose or furanose, possess 3,7-dioxabicyclo[4.1.0]heptane (**67**) and 3,6-dioxabicyclo[3.1.0]hexane (**68**) basic skeletons, respectively. 2,3-Anhydro-pyranoses usually adopt 5H_O or ${}^O H_5$ and 3,4-anhydropyranoses adopt 1H_O and ${}^O H_1$ conformations in the ground state.

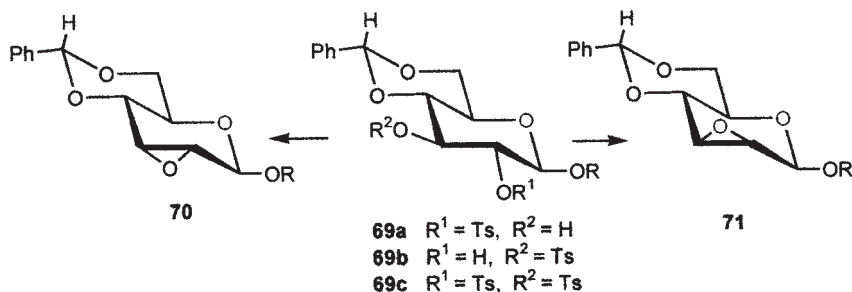


However, other conformations, such as the *B*, *S*, *H*, and *E* forms have been evidenced by 1H NMR studies, X-ray measurements, and calculations,^{269–271} and their important role in controlling the course of their reactions emphasized. Small energy differences between individual conformations are particularly evident with furanoses, which makes these systems very flexible. Consequently, clear interpretations from their NMR spectra may be difficult.

Epoxy sugars are frequently used as starting compounds in the synthesis of sugar derivatives (compare [Section IV](#)) such as halo, amino, azido, thio, deoxy, and branched-chain derivatives. The oxirane ring is in general more reactive than the oxetane or oxolane ring. It is opened with nucleophiles under base or acid catalysis. On the other hand, the oxirane ring remains unattacked under the conditions of catalytic debenzoylation on palladium,

in acylations and alkylations in the presence of bases, and in some cases during the hydrolysis of tosylates or replacement of a tosyloxy group by nucleophiles.

All configurational isomers of 2,3- and 3,4-anhydrohexopyranoses have been described. Generally, they adopt more or less flexible half-chair conformations (*H*) dependent on the absence or presence of an additional fused ring. Examples of the latter compounds are methyl 2,3-anhydro-4,6-*O*-benzylidene- α - and β -hexopyranosides of the *allo* **70**,^{272,273} *manno* **71**,^{273–275} *gulo*,^{276,277} and *talo*²⁷⁶ configurations.



The properties of various flexible 2,3- and 3,4-anhydropyranoses, and their deoxy derivatives have been studied.^{278–293} Methyl 2,3-anhydro-4-deoxy- α -DL-*ribo*-hexopyranosides exist potentially in seven low-energy conformers,²⁹⁴ (compare Ref. 295), as compared to the almost rigid 4,6-*O*-benzylidene derivatives, such as **70** and **71**. Related anhydrides, such as 2,3-anhydro-D-ribofuranosides,^{296–301} 2,3-anhydro-L-erythrofuransides,^{302,303} 3,4-anhydroketoses,^{304–308} and branched-chain sugar epoxides³⁰⁶ have also been described and been prepared by the following general methods:

(a) Intramolecular $\text{S}_{\text{N}}2$ nucleophilic displacement of a leaving group, usually tosyloxy or mesyloxy, by a vicinal hydroxyl group that has been deprotonated by a base such as sodium methoxide^{275,276,302} (or ion exchanger²⁸⁷). In this reaction, the configuration at the sulfonyloxy-substituted carbon atom is inverted and a single epoxy derivative is formed,^{8,12} see **69a** \rightarrow **71**, **69b** \rightarrow **70**.

However, additional side reactions, such as cleavage of sulfonates, cross-ring isomerization of epoxides, and epoxide migration, may take place under suitable steric arrangement.³⁰⁹ Although both the diequatorial and diaxial arrangements of the hydroxyl and tosyloxy group generally results in ring closure, the diaxial arrangement is considerably more reactive when the reacting molecule is sterically less flexible or rigid. Thus, a careful conformational analysis is an effective tool for prediction of the reaction

course and stereochemistry of the oxirane ring. This is particularly true in cases when vicinal disulfonates are used as starting compounds for oxirane-ring closure;³⁰⁹ see **69c** \rightarrow **70**. The initial step before the ring-closure reaction is presumably the regioselective cleavage of one of the $\text{RSO}_2\text{--OC}$ bonds to release a free oxyanion. This is presumably the sulfonyloxy bond that is sterically more accessible for attack by a base (in some cases unexpected nonreactivity was observed³¹⁰). Nevertheless, the specific reaction conditions, nature of the base, and the solvent may play an important role.²⁷⁶

(b) Epoxidation of the double bond in unsaturated sugar derivatives, such as glycosides, with peroxy acids and dioxiranes, using conventional procedures. In contrast to the cyclization route, here two diastereoisomeric oxirane derivatives may be formed, in a ratio that depends on steric control of the oxidation, which may be affected by the solvent and the nature of the oxidizing agent.^{283,311,312}

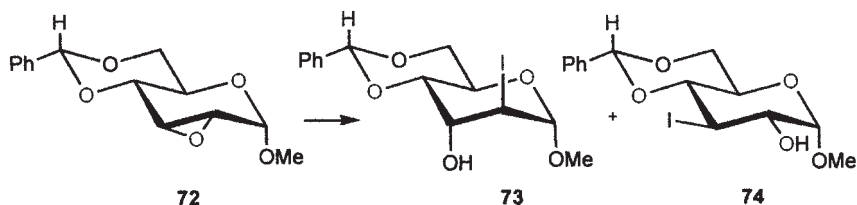
(c) The Mitsunobu reaction, which provides an alternative route for preparing oxirane derivatives that avoids the need for prior substitution of the starting vicinal diol.^{308,313–316} The tedious removal of side products (triphenylphosphine oxide and dialkylhydrazine dicarboxylate) constitutes a potential drawback of this method.

(d) The deamination of vicinal *trans*-amino alcohols²⁹⁸ and dehydration of vicinal diols via carbonate intermediates²⁷² are of interest but of less practical importance.

Ring-opening reactions of oxirane derivatives have been intensively studied from the mechanistic and preparative points of view.^{4,9,16} In general, these reactions give predominantly *trans*-diaxial products (according to the Fürst–Plattner rule), which may interconvert into the corresponding *trans*-diequatorial ones if the starting and/or final compound is sterically flexible. However, equatorial ring opening may occur, albeit it is more hindered and energetically less favored. Additional factors often play an important role in the regioselectivity of the reaction: the anomeric effect, polar effects of groups next to the oxirane ring, steric hindrance of the entering nucleophile and its repulsive interactions with the pyranose or furanose ring oxygen or other polar substituents in the molecule, control by the metal counterion of nucleophiles, metal chelation, acid or base catalysis, solvent effects, participation of the neighboring group,³⁰⁴ and so on. Consequently, the prediction of the reaction course and composition of the reaction mixture depends on proper assessment of the potential influence of the aforementioned factors.

The ring-opening reactions of 2,3-anhydroaldohexopyranoses reactions have been the most intensively studied with methyl 4,6-*O*-benzylidene-

hexopyranoside derivatives.^{1,317} As expected, these almost rigid compounds of the *allo* and *gulo* configurations are attacked by nucleophiles at C-2 to give products of the *altro* and *ido* configurations, respectively, by diaxial oxirane-ring opening. In comparison, the somewhat more flexible compounds of the *manno* and *talo* configurations give products of the *altro* and *ido* configurations, respectively, with nucleophiles attaching at C-3. Nevertheless, variable amounts of products of diequatorial oxirane-ring opening may appear in the reaction mixture.³¹⁸ Thus, for example, methyl 2,3-anhydro-4,6-*O*-benzylidene- α -D-allopyranoside (**72**) reacts with various Grignard reagents (prepared from alkyl iodides, bromides, chlorides) to afford different products in ether and tetrahydropyran. In addition to 2-iodo-D-*altro*- (**73**) and 3-iodo-D-*gluco*- (**74**) derivatives, C-methyl, deoxy, and unsaturated compounds were also isolated.³¹⁹



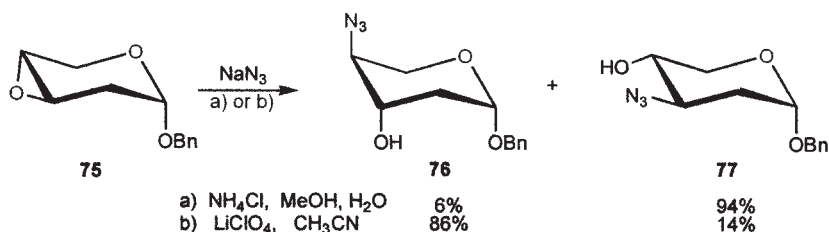
Other organometallic agents, such as lithium dimethylcuprate or 1,3-dithian-2-yl-lithium gave branched-chain sugars more straightforwardly.^{320,321} An unexpected diequatorial cleavage of the oxirane ring was observed with iodine in methanol, giving methyl ethers.³²² Unprotected 2,3-anhydropyranoses, including their glycosides, are less often used in synthesis because their ring-opening reactions usually lead to mixtures, due to the high steric flexibility of the systems and due to isomerization, for example epoxide migration (see Section V).

Anhydropyranoses having the *ribo* configuration are preferentially opened at C-3 with such nucleophiles as MgBr_2 , KCN, NaN_3 , NaOCH_3 , and LiH ;^{281,310,323} for the action of an intramolecular carboxylate nucleophile, see Ref. 324. With organometallic reagents, the regioselectivity is dramatically dependent on the nature of the agent,²⁸¹ as with $(\text{CH}_3)_2\text{CuLi}$, $(\text{CH}_3)_4\text{AlLi}$, and $(\text{CH}_3)_3\text{Al}$, especially for 4-deoxypentopyranoses.³²⁵ In comparison to these results, ethyl 2,3-anhydro-4,6-dideoxy-DL-*xylo*-pyranosides react with nucleophiles in alkaline as well as in acid solution to give mainly C-3 substitution products, while for DL-*ribo*-hexopyranosides a significant amount of opening at C-2 was also observed²⁸⁸ (compare Ref. 310). In certain cases, a sulfonyloxy group adjacent to the oxirane ring

can be replaced by azide ion³²⁶ (compare Ref. 327) or another nucleophile³²⁸ without affecting the oxirane ring (compare Ref. 305).

With furanose examples, attention has been focused mainly on 2,3-anhydropentoses.^{299,301–303,316,329–331} Here again, opening of the oxirane ring may occur both at C-2 and C-3 according to the nucleophile and the anomeric configuration.

When compared to 2,3-anhydroaldoses, the regioselectivity of the oxirane-ring cleavage in 3,4-anhydropyranoses is definitely less clear-cut. It is markedly dependent on the anomeric configuration and is also controlled by nature of the nucleophile as well as its counter cation. Both possible products are usually formed, and their ratio is significantly altered according to the reaction conditions^{270,278,282,289–293} as shown²⁹³ for the reaction of benzyl 3,4-anhydro-2-deoxy- α -D-erythro-hexopyranoside (**75**) \rightarrow **76** and **77**.



The ring-opening reactions of anhydroketoses may be directed by participation of a neighboring *trans*-acetoxy group.³⁰⁴ The primary hydroxymethyl group at C-6 may be substituted to afford a 6-deoxy-6-chloro or 6-thio derivative without affecting the oxirane ring.³⁰⁵ Reductive cleavage of the oxirane ring in 3,4-anhydrohex-2-uloses with zinc dust in methanol yields 3-deoxy derivatives.^{306,307}

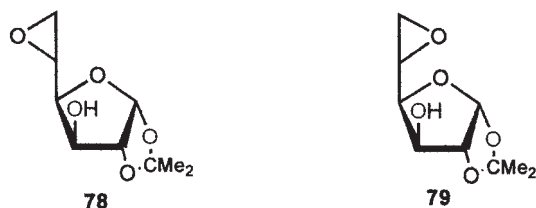
2. Exocyclic Oxirane Derivatives: 5,6-Anhydrohexofuranoses

These compounds have a similar steric arrangement of the oxolane ring as do ordinary derivatives of furanoses. Exocyclic oxirane-ring closure proceeds readily as compared to endocyclic epoxides because the required *trans*-orientation of the reacting groups is adopted without significant steric hindrance.

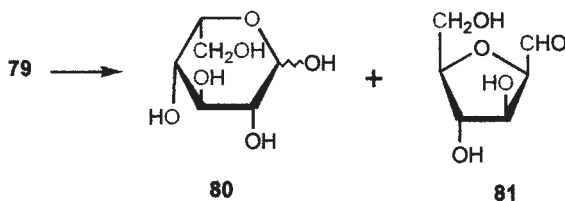
The standard methods detailed in the preceding section are suitable for the preparation of all isomers of 5,6-anhydrohexofuranoses. For example, the first compound of this class to be synthesized, 5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose,^{273,332} was prepared by selective tosylation (sulfonylation) of the parent furanose, followed by treatment with alkali; for application of this method, see Refs. 28, 333–335. Alternative

methods for the conversion of 5,6-diols into 5,6-epoxy derivatives involve the preparation of cyclic 5,6-sulfites, action of iodide ion, and treatment of the intermediate 6-iodo derivative with alkali.^{336a} Another method uses cyclic (5,6)-thiocarbonates and methyl iodide to form 6-iodohydrins as intermediates for the same purpose.^{336b}

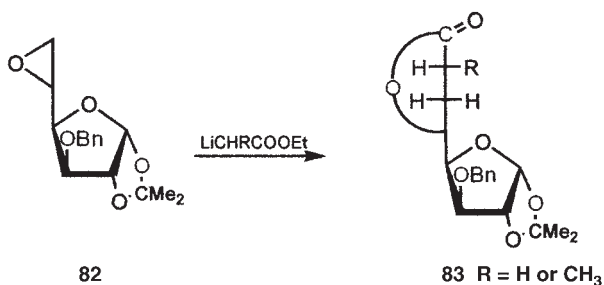
5,6-Anhydrohexofuranose derivatives of the following configurations have been described: *gluco* **78**,³³² *manno*,³³³ *ido* **79**,^{335,337} *allo*,³³⁸ and *galacto*.¹⁵³



Most of nucleophiles attack the 5,6-anhydrohexoses at C-6, in keeping with the expected regioselectivity of the normal S_N2 reaction.^{321,328,333,339,336a,340} However, this regioselectivity may be changed in reactions involving acid catalysis or metal-chelating interactions.^{339,341,342} Acid hydrolysis of 5,6-anhydro-1,2-*O*-isopropylidene- β -D-idofuranose (**79**) to give free L-idose (**80**) is very sensitive to reaction conditions, and several anhydro sugars were identified as side products (among them 2,5-anhydro-D-glucose, **81**). It is noteworthy that the oxirane ring is opened prior to cleavage of the isopropylidene acetal.³⁴¹



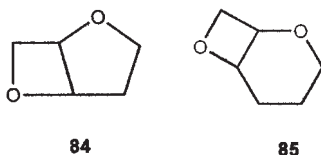
A direct transformation of the 5,6-oxirane ring into a 5,6-epithio ring^{337,340,343} or into an oxetane ring, with trimethylsulfoxonium iodide and potassium *tert*-butoxide has been described.³³⁴ Oxirane-ring opening of **82** was effected with chiral enolates to give 8,5-lactones **83**³⁴² and with higher alkylamines to give 6-alkylamino-6-deoxy derivatives.³⁴⁴



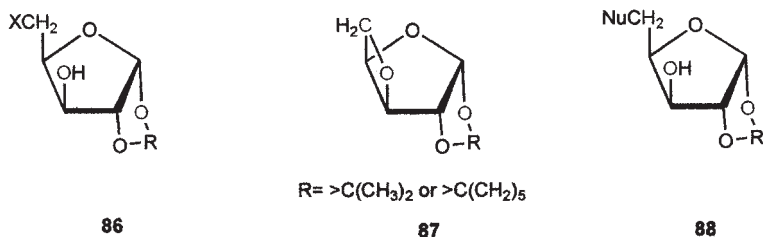
Ether-linked oligosaccharides have been prepared from 5,6-anhydro-D-glucose derivatives,³⁴⁵ and 5,6-anhydro sugars have also afforded various polysaccharides.^{338,346}

3. Oxetanes

Several types of anhydro-pentoses and -hexoses are known that contain a fused oxetane ring in the 2,6-dioxabicyclo[3.2.0]heptane (**84**) or 2,7-dioxabicyclo[4.2.0]octane (**85**) skeleton.

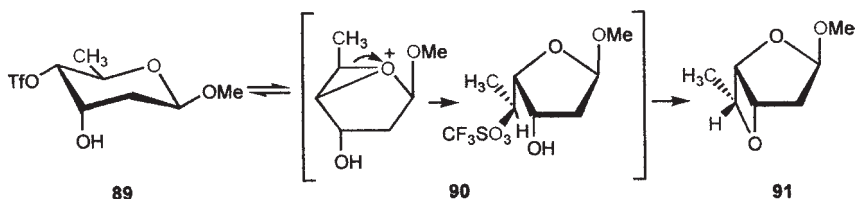


Among them, the first compound prepared and studied was 3,5-anhydro-1,2-*O*-isopropylidene- α -D-xylofuranose (**87**)³⁴⁷⁻³⁴⁹ and its 1,2-*O*-cyclohexylidene analogue.³⁵⁰ Formation of the oxetane ring is based on the internal substitution of an conventional leaving group X at C-5, or surprisingly, also phthalimido group in **86**,³⁵¹ for application of the Mitsunobu reaction, see Ref. 349.

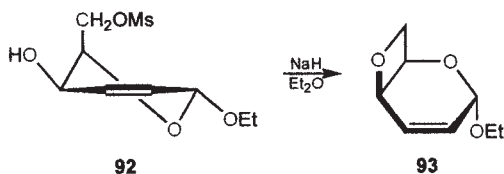


The oxetane ring of **87** is opened exclusively at C-5 by various nucleophiles under alkaline or acid reaction conditions, even with strong acids, to give **88** without impairing the 1,2-acetal grouping. This high regioselectivity can be accounted for by disfavored attack of the nucleophile at C-3. Polymerization of 3,5-anhydro-1,2-*O*-isopropylidene- α -D-xylofuranose gave (3 \rightarrow 5)-D-xylan.³⁵²

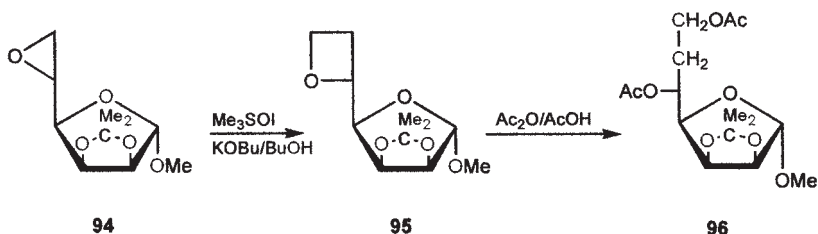
Heating the trifluoromethanesulfonate **89** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine gave methyl 3,5-anhydro-2,6-dideoxy- β -D-xylohexofuranoside **91**. This rearrangement involves oxane-ring contraction **90** followed by internal sulfonate displacement.³⁵³



The 4,6-anhydro derivative **93** has been reportedly prepared from ethyl 2,3-dideoxy- α -D-*threo*-hex-2-enopyranoside by mesylation at C-6 to give **92** and action of base;³⁵⁴ in a similar way a 4,6-anhydro- α -D-galactopyranosyl component was built into a nonreducing disaccharide.³⁵⁵

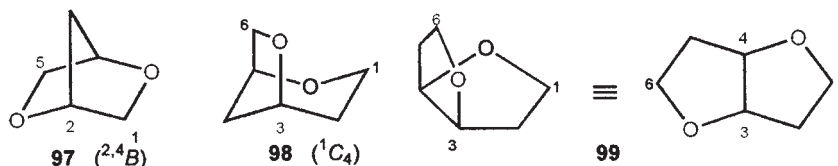


The exocyclic 5,7-anhydro-6-deoxyheptose **95** was prepared from the corresponding 5,6-anhydrohexose **94** and the oxetane ring was regioselectively cleaved at C-7 to give³³⁴ heptose **96**.



4. Oxolanes^{4,11}

These compounds, namely 2,5-anhydro- and 3,6-anhydro-aldoses may exist in bicyclic form, including the 2,5-dioxabicyclo[2.2.1]heptane (**97**), 2,6-dioxabicyclo[3.2.1]octane (**98**), and 2,6-dioxabicyclo[3.3.0]octane (**99**) basic skeletons, respectively, or as monocyclic oxolane derivatives possessing a free aldehyde group. In the latter case, a suitably oriented hydroxyl group is not disposed to form a furanose or pyranose ring with the free aldehyde group.

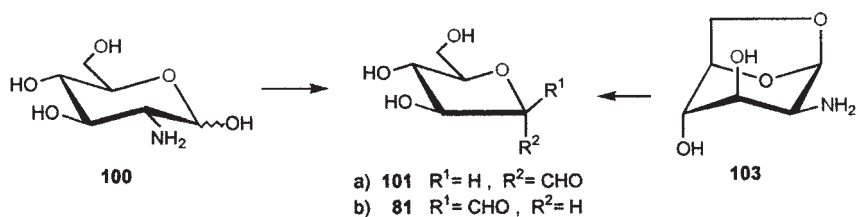


Since the oxolane ring is relatively stable toward acids and bases, the reactivity of these anhydro sugars is predetermined mainly by the presence of a free or potential aldehyde group.

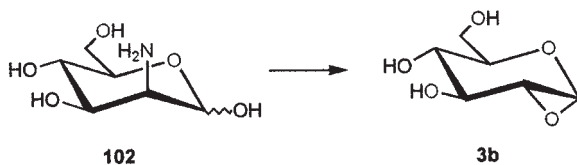
2,5-Anhydropentoses of all configurations have been described: *L-arabino*,³⁵⁶ *D-lyxo*,³⁵⁷ *D-ribo*,³⁵⁷ and *D-xylo*.³⁵⁷ Among the 2,5-anhydro-hexoses, the longest known is 2,5-anhydro-D-mannose (once named chitose, **101**),^{358–360} prepared by deamination of 2-amino-2-deoxy-D-glucose (**100**). Other isomers are the 2,5-anhydro derivatives of D-allose,^{361,362} D-altrose,³⁶² L-idose,^{363,364} D-glucose^{365,366} (compare Ref. 367), and L-talose.³⁶⁸ In general, almost all 2,5-anhydro sugars are syrupy or amorphous compounds, and are not very stable on storage at room temperature.

The aforementioned anhydro sugars and their derivatives were prepared by:

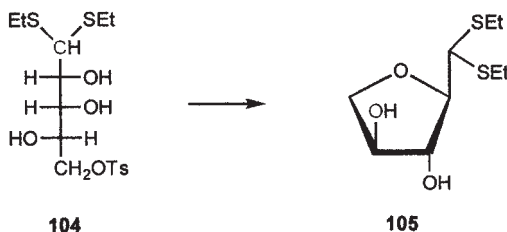
(a) Deamination of 2-amino-2-deoxyaldoses by means of nitrous acid in aqueous or acetic acid solution. This one-step method is recommended for preparing unsubstituted 2,5-anhydrohexoses, particularly 2,5-anhydro-D-mannose.^{358–360} Mechanistic studies revealed that the deamination with nitrous acid proceeds via diazonium and carbenium ions (mainly via a 1,2-antiparallel shift), and is most likely controlled by the most stable conformation of the starting amino sugar. Thus, 2-amino-2-deoxy-D-glucose (**100**) gives 2,5-anhydro-D-mannose (**101**), while 2-amino-2-deoxy-D-mannose (**102**) is converted into D-glucose by way of the intermediate 1,2-anhydro- α -D-glucopyranose (**3b**).²⁷ When mercuric oxide was used as the deaminating agent, 2,5-anhydro-D-glucose (**81**) was allegedly isolated.³⁶⁵



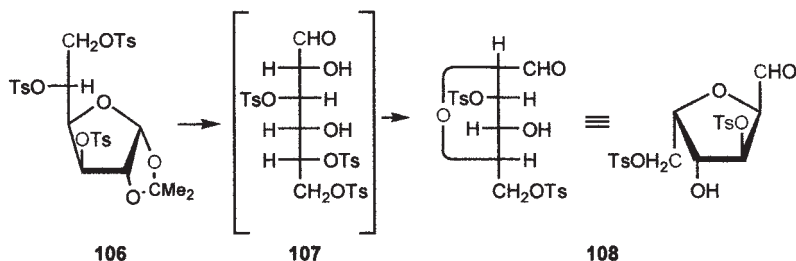
Nevertheless, compound **81** was definitely obtained later by deamination of 2-amino-1,6-anhydro-2-deoxy- β -D-mannopyranose (**103**) with nitrous acid, and was identified by reduction to 2,5-anhydro-D-glucitol.³⁶⁶ An analogous deamination was performed with 2-amino-1,6-anhydro-2-deoxy-3-*O*-tosyl- β -D-altropyranose to give, after detosylation, 2,5-anhydro-D-allose.³⁶¹



(b) Tosylation of aldopentose dithioacetals in pyridine yields the corresponding dithioacetals (**104** \rightarrow **105**) of 2,5-anhydropentoses, which may be converted into aldehyde forms or their acetals.^{357,369} A novel access to anhydro dithioacetals involves the synthesis of 2,5-anhydro-D-mannose derivatives by way of an intermediary dithioacetal *S*-oxide.³⁷⁰

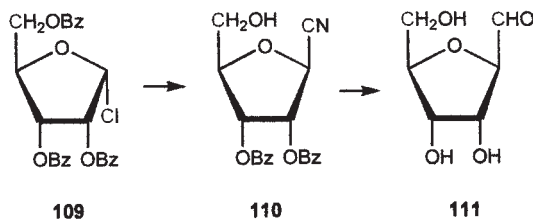


(c) Solvolysis of tosylated 1,2-*O*-isopropylidene- α -D-glucofuranose (**106**) in methanolic hydrogen chloride, probably proceeding via intermediate **107** gives the 2,5-anhydro-L-idose derivative **108** containing reactive tosyloxy groups suitable for further transformations.^{363,368} A similar solvolysis was performed with an analogous 5-mesylate.³⁷¹



In relation to these solvolyses is the formation of free 2,5-anhydro-L-idose upon attempted hydrolysis of 5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose.³⁶⁴

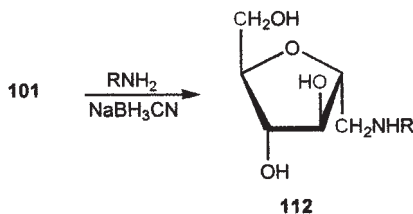
(d) An additional potential route involves the reaction of glycofuranosyl halides (**109**) or the corresponding 1-acetates with $\text{Hg}(\text{CN})_2$ or trimethylsilyl cyanide, respectively. The cyano group in the glycofuranosyl cyanides **110** thus obtained is converted by reduction into formyl group (**109–111**).^{362,372}



(e) For other less-frequently used methods, such as oxidative glycol cleavage of the side chain of a 3,6-anhydro-D-mannitol derivative, see Ref. 11.

As already mentioned, the oxolane ring in 2,5-anhydro sugars is relatively stable, being cleaved only by strong acids, usually after initial dehydration to a furan system.³⁷³ Consequently, the free aldehyde group or that involved in a hemiacetal group is responsible for most of the common reactions. From conformational analysis it follows that only 2,5-anhydrohexoses having the *cis* arrangement of the aldehyde and C-5 hydroxymethyl group, and 2,5-anhydropentoses of the *arabino* and *lyxo* configurations form 1,6- and 1,5-hemiacetals, respectively. The free aldehyde group confers enhanced instability [compare the decomposition of 2,5-anhydro-D-mannose (**101**) in the presence of weak bases³⁷⁴] and forms acetals³⁶¹—not the corresponding glycosides—when treated with methanolic hydrogen chloride, and also yields hydrates with water,³⁶⁰ and hemiacetals with alcohols in neutral solutions. The free aldehyde group also facilitates β -elimination of a hydroxyl group. Methyl glycosides are extremely acid labile, and are converted into acetals under glycosidation conditions.

On the other hand, the high reactivity of the aldehyde or potential aldehyde group enables many condensation reactions, leading to *N*-alkylamino compounds (**112**) and analogous *C*-alkyl derivatives.^{359–361}

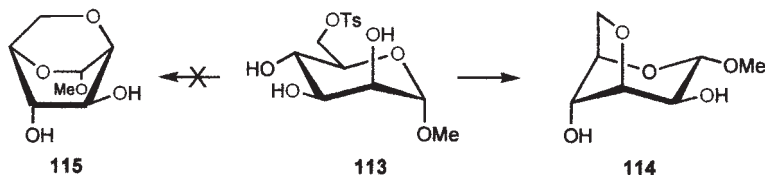


Most anhydro compounds of this class are derivatives of 3,6-anhydroaldohexoses. All eight possible configurations of the 3,6-anhydroaldohexoses have been described.^{2,4} According to their configuration and conformation,^{375,376} some of them exist in bicyclic pyranose (**98**) or bicyclic furanose (**99**) structures. Thus, 3,6-anhydro derivatives of glucose and mannose can adopt both the pyranose and *cis*-fused furanose form, those of galactose and talose only the pyranose form, and those of gulose and idose only the *cis*-fused furanose form. In comparison, free 3,6-anhydro-D-allose and -D-altrose can only exist in the acyclic form.^{377,378} Some *trans*-fused 3,6-anhydro derivatives of the allose and galactose configurations have been prepared.³⁷⁹

In addition to 3,6-anhydroaldohexoses, some anhydroketoses, for example 3,6-anhydro-D-fructose, are known.^{380,381}

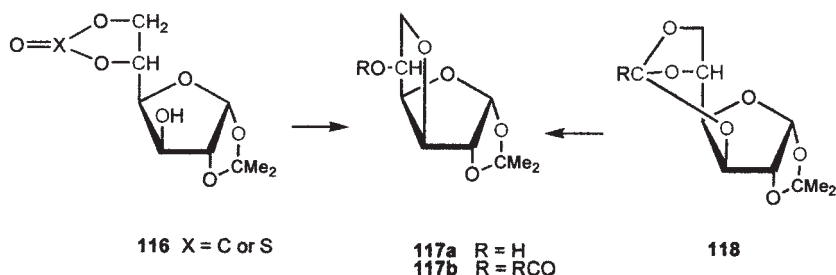
The following methods have been used for the synthesis of 3,6-anhydrohexoses:

(a) Selective tosylation at C-6 [also substitution by $(\text{Me}_2\text{N})_3\text{P}$ or halogen] of various alkyl hexo-pyranosides, -furanosides, and 1,2-*O*-isopropylidene derivatives, followed by treatment of the intermediate 6-tosylates (or the corresponding halides) with strong bases (for example, sodium methoxide).^{379,382,383} The trend of preferential formation of the oxolane before the oxane ring is demonstrated by the conversion of methyl 6-*O*-tosyl- α -D-mannopyranoside (**113**) into 3,6-anhydride **114** but not into 2,6-anhydride **115**.³⁷⁶



In this connection it is noteworthy that not only a free hydroxyl group at C-3 but also a benzyloxy and methoxy group can act as internal nucleophiles in formation of the 3,6-anhydride bond.³⁸⁴ An alternative to this method is the substitution of the tosyloxy group at C-3 by the primary hydroxymethyl group at C-6 involving the intermediary formation of 2,3- or 3,4-oxirane ring (see Section V).

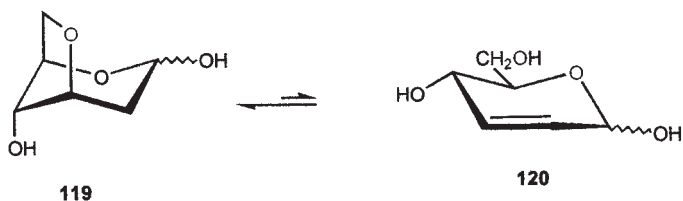
(b) Basic solvolysis of 5,6-thionocarbonates, sulfates, or sulfites of the corresponding furanosides **116**, giving exclusively 3,6-anhydrohexofuranose derivatives **117**.³⁸⁵ The cyclic 3,5,6-orthoester **118** reacts in an analogous way.³⁸⁶ Treatment of 2,3-di-*O*-acyl-D-glycopyranosides with trifluoromethanesulfonic acid in 1,2-dichloroethane is of limited use.³⁸⁷ A photochemical formation of a substituted oxolane ring has been described.³⁸⁸



(c) Mercaptolysis of agar is recommended as a convenient method for preparing 3,6-anhydro-L-galactose diethyl dithioacetal.³⁸⁹

Conformational analysis explains why the relatively strained 2,6-dioxabicyclo[3.2.1]octane skeleton **98** of 3,6-anhydro-D-gluco- and -D-mannopyranose tends to recyclize rapidly in the presence of methanolic hydrogen chloride into the less-strained 2,6-dioxabicyclo[3.3.0]octane skeleton **99** of the 3,6-anhydrohexofuranose. Obviously, such rearrangement cannot take place with the *galacto* or *talo* configurations, and consequently, acyclic acetals are formed.^{390,391}

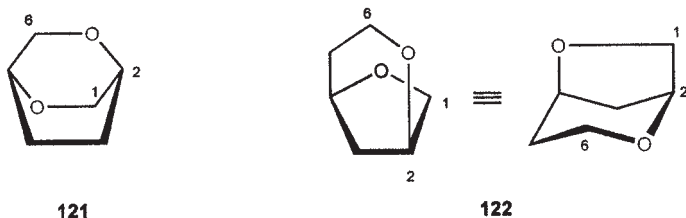
As the glycosidic bond in ordinary methyl 3,6-anhydrohexofuranosides is more readily cleaved in acid solution than the 3,6-anhydro ring, free anhydrohexoses are released and exhibit the reactivity of equilibrated pyranose and furanose forms.^{376,392} However, interesting behavior is observed with 3,6-anhydro-2-deoxy-D-*arabino*-hexose ("isoglucal," **119**).^{393–395} In weakly basic solution an equilibrium shifted to the left is established between "isoglucal" (**119**) and 2,3-dideoxy-D-*erythro*-hex-2-enopyranose (**120**).



Selective monotosylation of methyl 3,6-anhydro- α -D-mannofuranoside and the corresponding β -D-*gluco*- and β -L-*gulo*-glycosides gives preferentially the 5-tosylates, whereas with 3,6-anhydro- α -D-glucofuranoside no significant selectivity of tosylation was observed.³⁷⁶ The preparation of new nucleoside analogs is a relevant example of the utilization of 3,6-anhydrohexoses.³⁹⁵

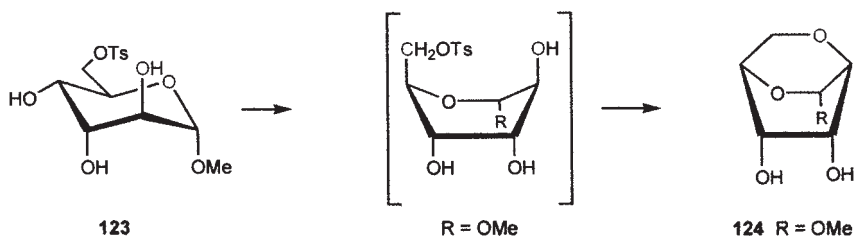
5. Oxanes

a. 2,6-Anhydrohexoses.—This class of compounds includes both pyranose and furanose derivatives, which adopt either the rigid 2,5-dioxabicyclo[2.2.2]octane skeleton (**121**) with the pyranose ring in the ^{2,5}*B* or *B*_{2,5} conformation or the 2,6-dioxabicyclo[3.2.1]octane skeleton (**122**) with limited flexibility of the oxane ring in the ⁴*C*_O conformation.



Pyranoid examples have been prepared in all possible configurations: *altro*,^{396,397} *ido*,^{398,399} *manno*,^{398,400} and *talo*.^{185,396} From the furanose group, 2,6-anhydro-D-mannofuranose and its derivatives are known.^{366,401,402}

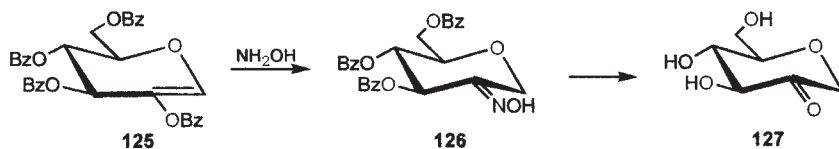
The first compound of this group, methyl 2,6-anhydro- α -D-altropyranoside (**124**), was prepared by the action of sodium methoxide on the corresponding 6-tosylate **123**.³⁹⁷ This method was later applied to the preparation of other 2,6-anhydrohexoses having a *cis*-oriented hydroxymethyl group and a free hydroxyl group at C-2.



An alternative synthesis is based on the replacement of the mesyloxy group at C-2 by the hydroxymethyl group with inversion of configuration.⁴⁰⁰

2,6-Anhydro- β -D-mannose was obtained by deamination of 2-amino-1,6-anhydro- β -D-glucopyranose.³⁶⁶ Treatment of 1,6-anhydro derivatives of β -D-glucopyranose and β -D-galactopyranose with diethylaminosulfur trifluoride (DAST) gave the corresponding 2,6-anhydrohexopyranosyl fluorides.¹⁸⁶ In a similar way, methyl 2,6-anhydro-2,3-isopropylidene- α,β -D-talopyranosides were obtained from 1,6-anhydro-2-*O*-mesyl- β -D-galactopyranose upon attempted substitution of the mesyloxy group with KF in methanol.¹⁸⁵ A substituted 2,6-anhydro-5-azido-5-deoxy-L-*allo*-heptose derivative was prepared by cycloaddition from an L-*allo*-heptose derivative and acetone.⁴⁰³

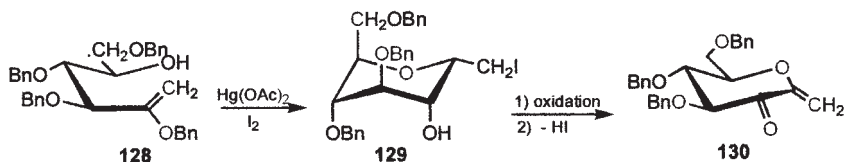
b. 1,5-Anhydroketoses.—Only a few anhydroketoses of this type have been prepared and their reactions studied. Among them, of particular interest is 1,5-anhydro-D-fructose (**127**)^{404a} which is available from 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol (**125**) via the 2-oxime **126**,^{404b} or alternatively by bacterial oxidation of 1,5-anhydro-D-glucitol,⁴⁰⁵ or by degradation of starch and glycogen by glucan lyase (EC 4.2.2.13).^{406,407} It is the first anhydrofructose found in Nature.⁴⁰⁸



1,5-Anhydro-D-fructose (**127**) forms a dimeric structure of two isomeric spiroketals^{404c,409} and influences some glucose-metabolizing enzymes.⁴¹⁰ Its acetylation with acetic anhydride in pyridine results in β -elimination of acetic acid to give a D-*glycero*-hex-3-en-2-ulose derivative.⁴⁰⁴ 1,5-Anhydro-4-deoxy-D-*glycero*-hex-1-en-3-ulose^{411,412} and the corresponding pent-3-ulose⁴¹³ were identified in the complex mixture resulting from the

pyrolysis of cellulose and xylan, respectively. 1,5-Anhydro-D-tagatose was prepared by oxidation of 6-*O*-protected 1,5-anhydro-3,4-*O*-isopropylidene-D-galactitol with tetrapropylammonium perruthenate⁴¹⁴ and subsequent deprotection. Free 1,5-anhydro-hex-2-uloses exist in aqueous solution in equilibria between a 2,5-dioxabicyclo[2.2.2]octane hemiacetal form and dimeric forms, as indicated by NMR and IR spectra.

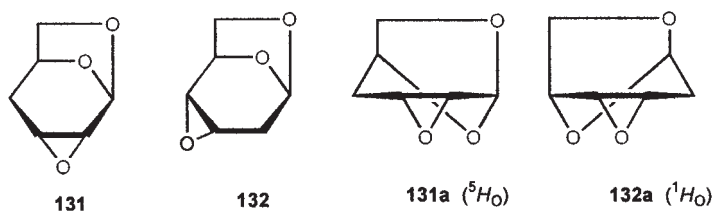
A derivative (**130**) of 2,6-anhydrohept-1-en-3-ulose, prepared as an unstable intermediate by a three-step synthesis from D-*gluco*-hept-1-enitol (**128**) via 1-iodo derivative **129**, undergoes spontaneous cyclodimerization.⁴¹⁵



IV. DIANHYDROALDOSES AND KETOSES

1. 1,6:2,3- and 1,6:3,4-Dianhydrohexopyranoses^{3,13}

These dianhydrohexoses constitute a complete series of eight isomers having rigid tricyclic skeletons, such as 3,8,9-trioxatricyclo[4.2.1.0^{2,4}]nonane and 3,7,9-trioxatricyclo[4.2.1.0^{2,4}]nonane, respectively, as represented here by 1,6:2,3-dianhydro-4-deoxy- (**131**) and 1,6:3,4-dianhydro-2-deoxy- β -D-*ribo*-hexopyranose (**132**).



In the crystalline state, as well as in solution, dianhydrohexopyranoses adopt the ⁵H_O (for example, **131a**) or ¹H_O (**132a**) conformations, as shown by X-ray analysis^{416,417} and NMR spectra.^{418,419}

The 1,6-anhydride bond is rather stable toward bases, permitting not only highly selective reactions of free hydroxyl groups, such as acylation, sulfonylation, and alkylation by conventional methods, but also by selective nucleophilic attack of the oxirane ring. On the other hand, the 1,6-anhydride bond is cleaved in acid solutions (concurrently with the

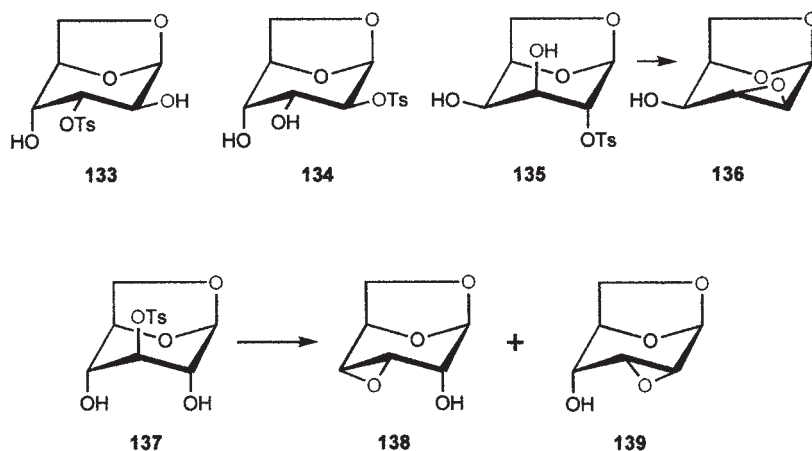
oxirane ring) unless it is stabilized by an electron-withdrawing substituent at C-2.^{420,421}

Dianhydrohexopyranoses having a hydroxyl group *trans*-oriented toward the oxirane ring undergo epoxide migration in alkaline solution, even at room temperature (see Section V). The following dianhydrohexopyranoses have been described (for physical data, see Ref. 422): 1,6:2,3-dianhydro- β -D-allo-,^{423,424} D-gulo-,^{425,426} D-manno-,^{426,427} and D-talo-pyranose;^{417,427,428} 1,6:3,4-dianhydro- β -D-allo-,^{423,424} D-altro-,^{425,429} D-galacto-,^{178,425,430} and D-talo-pyranose.^{27,417,431,432}

Four corresponding deoxy derivatives have also been prepared: 1,6:2,3-dianhydro-4-deoxy- β -D-*lyxo*-,^{432,433} and -D-*ribo*-hexopyranose,^{169,432} and 1,6:3,4-dianhydro-2-deoxy- β -D-*lyxo*-, and -D-*ribo*-hexopyranose.^{169,432}

Several methods are used for preparing dianhydrohexopyranoses:

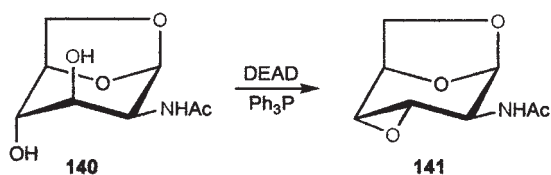
a. The most frequently used method is based on intramolecular displacement of a tosyloxy group by a *trans*-oriented vicinal hydroxyl group ionized in basic solution, usually sodium methoxide in methanol;^{8,427,429} *trans*-oriented vicinal disulfonates react in a similar way.⁴²³ An alternative method starts with halohydrins^{158,417,434} prepared from unsaturated derivatives. A *trans*-diequatorial arrangement of both reacting groups is less prone (for instance, in **133**) or even reluctant (in **134**) to undergo any oxirane-ring closure, as compared to the optimal *trans*-diaxial arrangement (**135** \rightarrow **136**) and (**137** \rightarrow **138** and **139**).^{8,423,424}



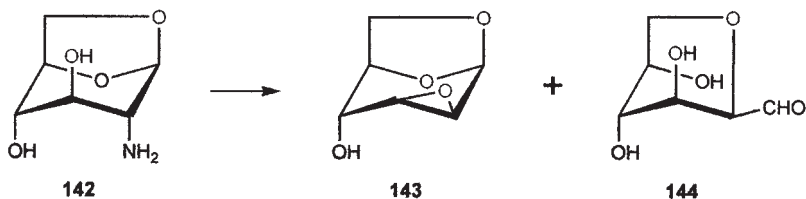
b. By epoxidation with peroxy acids of a double bond in the corresponding derivatives of 1,6-anhydro- β -D-hexopyranoses. The oxirane ring is

preferentially oriented *exo* due to steric hindrance exerted by the 1,6-anhydro bond.^{169,434}

c. Application of the Mitsunobu reaction constitutes a potential alternative method, thus far not frequently used. From 1,6-anhydro- β -D-glucopyranose (**22**) a mixture of the 3,4-*allo* (**138**) and the corresponding 1,6:3,4-dianhydro- β -D-galactopyranose was formed.³¹³ The rather unexpected formation of 1,6:3,4-dianhydro- β -D-allopyranose (**138**) indicates possible activation of the sterically hindered hydroxyl group at C-3 by diethyl azodicarboxylate (compare Ref. 435). Similarly, the *altro* amino-epoxide **141** was obtained from 2-acetamido-1,6-anhydro-2-deoxy- β -D-mannopyranose (**140**) as the sole product.⁴³⁶

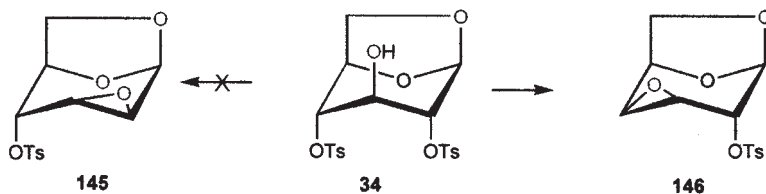


d. The aminodeoxy derivatives of 1,6-anhydro- β -D-hexopyranoses having a *trans*-diaxial arrangement of a hydroxyl and amino group undergo deamination with nitrous acid to give mainly oxirane derivatives, for example **142** gives 1,6:2,3-dianhydro- β -D-mannopyranose (**143**) and 2,6-anhydro-D-mannose (**144**). This reaction is of interest from the mechanistic point of view but is of limited preparative value.^{185,366}

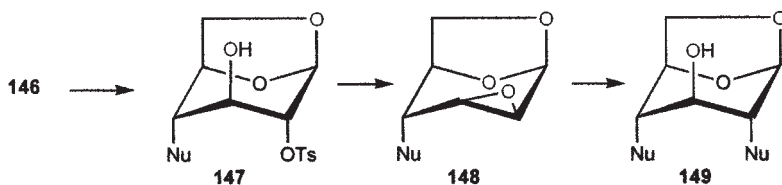


A characteristic feature of the dianhydrohexopyranoses is their steric rigidity. Consequently, they usually react with high and predictable regio- and stereoselectivity, mainly by diaxial cleavage of the oxirane ring. Thus, they became versatile starting materials for synthesis of various carbohydrates as well as noncarbohydrate structures. The most important compounds are 1,6:3,4-dianhydro-2-*O*-tosyl- β -D-galactopyranose (**146**), the *manno* epoxide **143**, the *altro* epoxide **159**, and the 2,3- and 3,4-anhydro-*allo* epoxides **138** and **139**. The tosyl epoxide **146** (for its crystal structure,

see Refs. 437, 438) is readily available as a single product from 1,6-anhydro- β -D-glucopyranose (**22**) by selective tosylation and subsequent treatment of the 2,4-ditosylate **34** with sodium methoxide; isomer **145** is not formed.¹⁷⁶

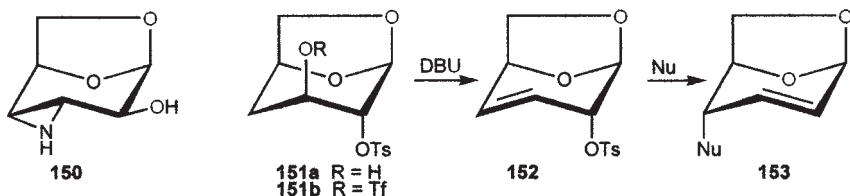


This highly regioselective formation of the oxirane ring can be accounted for (a) by repulsive polar interactions between the intermediary oxide ion at C-3 and the oxygen atom of the 1,6-anhydro bond, and (b) by better nucleofugacity of the leaving tosyloxy group at C-4 than at C-2. Tosyl epoxide **146** is cleaved under acid or base catalysis by a broad range of nucleophiles,^{3b,13} such as water,⁴²⁰ alcohols,^{439–444} thiols,⁴³⁰ sodium thiocyanate,⁴⁴⁵ phosphorodithioic acid,⁴⁴⁶ halogen acids,^{421,445,447,448} ammonia,⁴⁴⁹ amines,^{440,450,451} azide,^{452–454} carboxylic acids,⁴²⁹ organo-metallics,^{455–459} or diborane⁴⁶⁰ to give 4-substituted derivatives (**147**) of 1,6-anhydro- β -D-glucopyranose. When the ring opening is performed in basic solution, the initial product, an oxyanion at C-3, undergoes further intramolecular substitution to give 1,6;2,3-dianhydro- β -D-mannopyranose substituted at C-4 (**148**) or a 2,4-disubstituted 1,6-anhydro- β -D-glucopyranose **149** as the final product of a multistep reaction sequence.^{421,453,461–463}

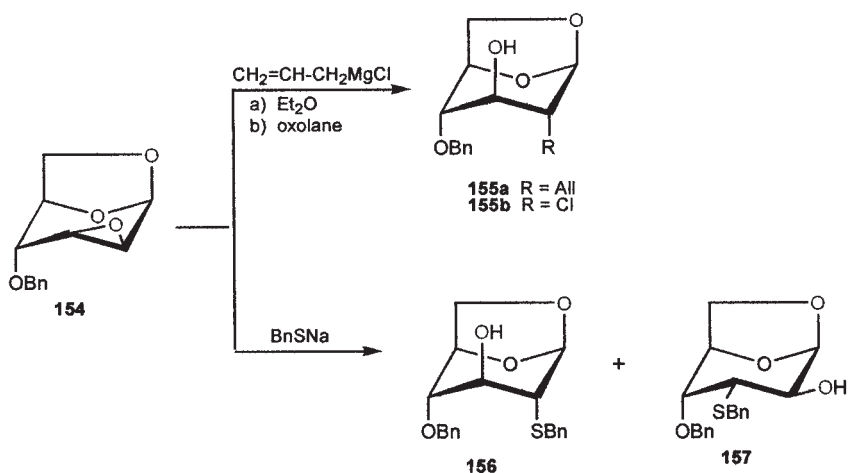


Thus, a complex mixture of amino and epimino derivatives is formed following ammonolysis of tosyl epoxide **146** or ditosylate **34**, containing mainly 2,4-diamino-2,4-dideoxylevoglucosan **149** (Nu = NH₂) and 1,6-anhydro-3,4-dideoxy-3,4-epimino- β -D-altropyranose (**150**).⁴⁴⁹ The preparation of two isomeric 4-deoxyepoxides **131** and **148** (Nu = H)^{460,464} and of 2,3- and 3,4-unsaturated derivatives **152** and **153** also starts with tosyl epoxide **146** ($\rightarrow \text{151a} \rightarrow \text{151b} \rightarrow \text{152} \rightarrow \text{153}$).^{460,465–467} Among them, 1,6-anhydro-3,4-dideoxy-2-O-tosyl- β -D-erythro-hex-3-enopyranose (**152**),^{467,468} and the analogous 2-chloro-2-deoxy derivative⁴⁶⁹ are alkylating compounds

in which the leaving tosyloxy or chloro group can be replaced by nucleophiles under stereoselective allylic rearrangement (**152** \rightarrow **153**).

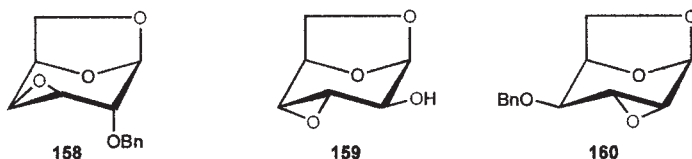


Another valuable compound for the synthesis of 2-substituted derivatives of levoglucosan is the *O*-benzyl mannoepoxide **154**.^{426,434,470} The cleavage of its oxirane ring takes place at C-2 with high regioselectivity (except with thiols,⁴⁷¹ compare Refs. 472, 473) by using the following nucleophiles: water,⁴⁷⁴ alcohols,^{475,476} NH_3 ,^{477,478} benzylamine,⁴³⁵ azide,^{454,470,479-481} (compare Ref. 453), fluoride,⁴²¹ iodide,⁴³² complex hydrides¹⁰⁸ (compare Ref. 482 for hydrogenolysis), and organometallics.⁴⁸³⁻⁴⁸⁷ A solvent dependence was observed for the reaction of **154** with allylmagnesium chloride in ether (see **155a**) or in oxolane (see **155b**).⁴⁸⁶ An anomalous oxirane-ring opening was observed⁴⁷¹ with sodium phenylmethanethiolate (**154** \rightarrow **156** and **157**).



In general, diaxial oxirane-ring cleavage also takes place with other oxirane derivatives, for example 1,6:3,4-dianhydro-2-*O*-benzyl- β -D-galactopyranose (**158**), to give 4-substituted 1,6-anhydro-D-glucopyranoses.^{435,452,475,476,494} Both free and *O*-substituted alloepoxides **138** and **139**

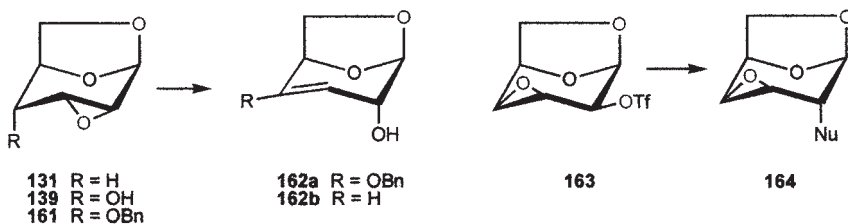
give the corresponding 3-substituted derivatives.^{435,442,488–491} Free or substituted altroepoxide **159** is a prospective compound for preparing 3-substituted 1,6-anhydro- β -D-mannopyranoses, such as 3-deoxy-3-fluoro,⁴⁹² 3-deoxy,⁴⁹³ 3-amino-3-deoxy,^{435,494} and 3-deoxy-3-azido,^{184,494} derivatives. Treatment of guloeptide **160** with sodium azide gave 3-azido-3-deoxy derivative having the *D-galacto* configuration⁴⁹⁴ and with diethylaluminum cyanide the corresponding 3-C-cyano derivative, which readily isomerizes in basic solution to the more stable 1,6-anhydro-3-C-cyano- β -D-gulopyranose;^{495a} compare the unexpected ring-opening reaction of **160** with phenylmethanethiol (α -toluenethiol).^{495b}



Intramolecular oxirane-ring opening at C-4 substituted anhydride **148**, where Nu = $-\text{O}-(\text{CH}_2\text{CH}_2)_n\text{OH}$ or $-\text{O}-(\text{CH}_2)_n\text{NH}_2$, affords a new heterocyclic ring fused to 1,6-anhydro- β -D-hexopyranose.⁴⁴³

In the case of 1,6:2,3- (**136**) and 1,6:3,4-dianhydro- β -D-talopyranoses, the diaxial opening of the oxirane ring prevails, but a trend to diequatorial opening^{496–498} is apparent with 1,6:2,3-dianhydro-4-deoxy- and 1,6:3,4-dianhydro-2-deoxy- β -D-*lyxo*-hexopyranoses.^{169,432,493} Using 1,6:2,3- and 1,6:3,4-dianhydrohexopyranoses as starting compounds allowed the preparation of a complete series of 12 isomeric 1,6-anhydro-monodeoxy- β -D-hexopyranoses and 6 corresponding 1,6-anhydro-dideoxyhexoses,⁴⁹⁹ mainly by catalytic or complex hydride reductions.^{462,500}

Unsubstituted dianhydrohexoses having the *D-allo* and *D-talo* configurations, in which the hydroxyl group and oxirane ring have a *cis* relationship, as in **139**, decompose in hot aqueous potassium hydroxide, whereas the benzyl ether **161** forms enol ether **162a**.⁴²⁶ Treatment of 1,6:2,3-dianhydro-4-deoxy- β -D-*ribo*-hexopyranose **131** with butyllithium gives the unsaturated alcohol **162b**.^{169,501}

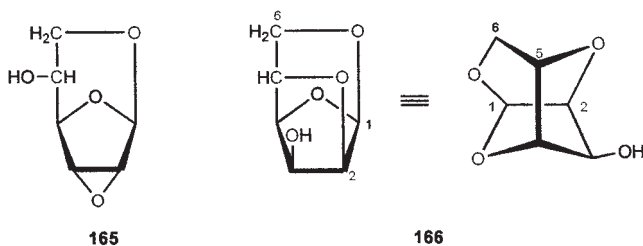


Unsubstituted 1,6:2,3- and 1,6:3,4-dianhydrohexopyranoses contain only one free hydroxyl group, either at C-4 or at C-2, respectively. Although these hydroxyl groups show different reactivity, they are readily oxidized,^{502,503} methylated,⁵⁰⁴ benzylated,^{470,505} and glycosylated⁵⁰⁶ to give functionalized dianhydrides. Replacement of sulfonyloxy groups in dianhydrohexopyranoses has not been studied systematically, but it was found that the trifluoromethanesulfonate **163** of 1,6:3,4-dianhydro- β -D-talopyranose reacts with various nucleophiles ($\text{Nu} = \text{F}^-$, N_3^- , and RS^-) to form the corresponding epoxy derivatives **164** of the D-galacto configuration.⁵⁰⁷

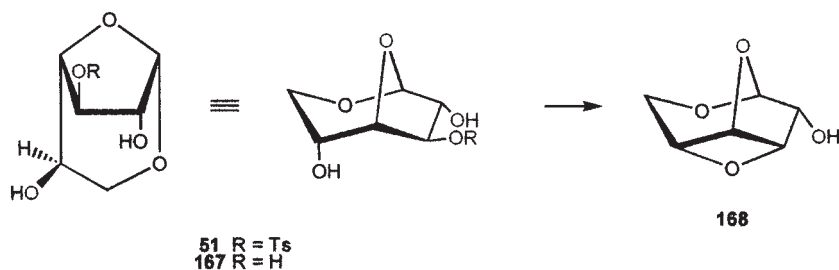
A new class of regio- and stereoregular 2,3- and 3,4-linked D-glucose polymers of the polyether type was synthesized by anionic polymerization of O-alkyl derivatives of 1,6:2,3-dianhydro- β -D-mannopyranose and 1,6:3,4-dianhydro- β -D-galactopyranose. These polymers constitute highly functionalized synthetic polymers that may be additionally modified by cleavage of the 1,6-anhydride bond to afford a large variety of polyglucose and polyglucitol derivatives of potential industrial application.⁵⁰⁸⁻⁵¹⁰

2. Miscellaneous Dianhydro Sugars Involving the Anomeric Carbon Atom in One of the Anhydro Bonds

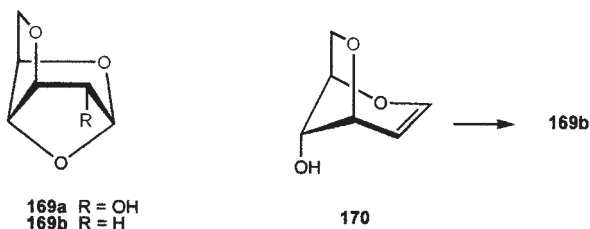
Some oxirane, oxetane, and oxolane derivatives of 1,6-anhydrohexoses are known, for example 1,6:2,3-dianhydro- β -D-allofuranose (**165**) and the corresponding α -L-talofuranose,²⁴³ 1,6:2,5-dianhydro- α -L-gulofuranose (**166**),^{511,512} 1,6:3,5-dianhydro- α -L-idofuranose,²⁴⁵ 1,6:3,5-dianhydro- α -L-gulofuranose,^{246,512} and 1,6:4,7-dianhydro-D-glycero- β -D-gulopyranose.²⁴⁹



Selective tosylation of 1,6-anhydro- α -D-galactofuranose (**167**) is favored for position C-3 because of steric accessibility and affords tosylate **51**. Treatment of **51** with base results in intramolecular displacement of the tosyloxy group by 5-hydroxyl group with the formation of 1,6:3,5-dianhydro- α -D-gulofuranose (**168**); the reaction involves closure of the oxetane and not the oxirane ring.²⁴⁶

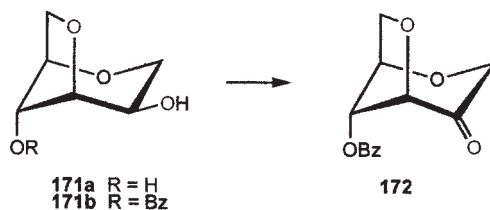


1,4:3,6-Dianhydro- α -D-glucopyranose (**169a**) has been identified as a minor product from the pyrolysis of D-glucose, amylopectin, and cellulose.^{513,514} Its 2-deoxy derivative (**169b**) was prepared by cyclization of the corresponding 1,5:3,6-dianhydro- α -D-arabino-hex-1-enitol (3,6-anhydro-D-glucal, **170**).⁵¹⁵



3. Miscellaneous Dianhydro Sugars Not Involving the Anomeric Carbon Atom in Anhydro Bonds

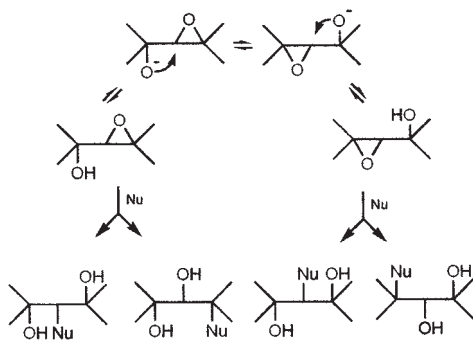
Most compounds of this type are derived from methyl hexosides: methyl 2,6:3,4-dianhydro- α -D-altropyranoside^{309,398,400,516} and methyl 2,5:3,6-dianhydro- α - and β -D-mannofuranosides.⁵¹⁷ From hexuloses, the synthetically useful 1,5:3,6-dianhydro-D-arabino-hex-2-ulose (**172**) has been prepared by regioselective monobenzoylation of 1,5:3,6-dianhydro-D-mannitol at C-4 (**171a** \rightarrow **171b**) followed by oxidation with tetrapropylammonium perruthenate.⁵¹⁸



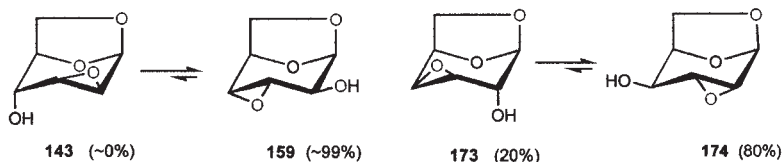
V. REARRANGEMENTS OF ANHYDRO SUGARS

1. Epoxide Migration

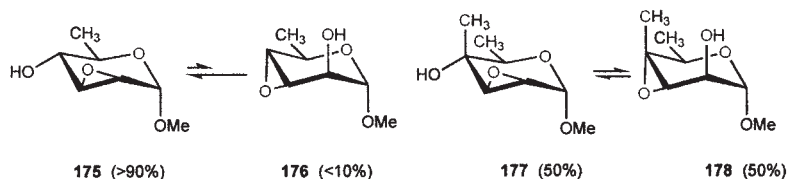
Epoxide migration^{8,12} is actually a nucleophilic attack of a vicinal oxide ion (originating from a hydroxyl group) on the *trans*-oriented oxirane ring within a sugar molecule, which results in formation of an isomeric epoxide. This reversible reaction is catalyzed by strong bases and proceeds with inversion of configuration only at the central carbon atom. It may be accompanied by competitive cleavage of the oxirane ring by an external nucleophile. Consequently, external basic nucleophiles, which are capable of deprotonating a hydroxyl group, can occasionally initiate the epoxide migration and finally effect the ring-cleavage of both isomeric epoxides and their conformers.



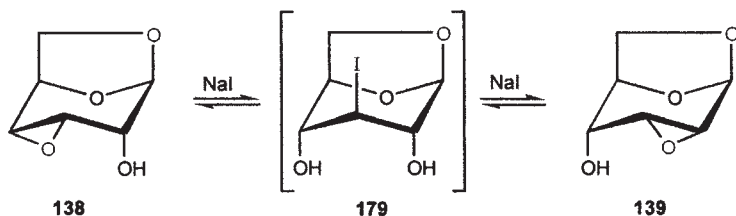
Potential factors controlling epoxide migration has been discussed by several authors; however, any prediction of the composition of the equilibrium mixture is only possible provided that a conformational analysis and energetic balance of the products is completely taken into account. The epoxide migration of rigid 1,6:2,3- (**143**, **174**) and 1,6:3,4-dianhydrohexopyranoses (**159**, **173**)^{420,425-427} takes place in dilute aqueous potassium hydroxide solution even at room temperature. This might be interpreted as a result of the dominating repulsive interaction between the *endo* oxirane ring and the oxygen atom of the 1,6-anhydro bond.⁵¹⁹ Interestingly, the benzylation of **143** with benzyl bromide in aprotic solvents in the presence of sodium hydride gives the corresponding benzyl ether **154**.⁴⁷⁰



On the other hand, the situation is more complex with flexible oxirane derivatives. This is clearly demonstrated by comparison of the equilibrium mixtures resulting after epoxide migration of different types of anhydro hexoses,^{278,286,304} their 6-deoxy derivatives **175**, **176**,⁵²⁰ branched-chain hexoses **177**, **178**,^{520,521} and anhydro hex-2-uloses.³⁰⁴

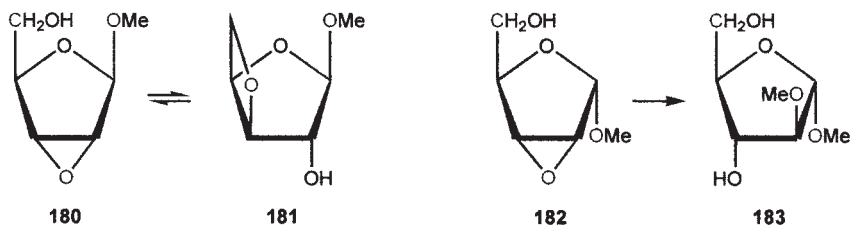


The isomerization of alloepoxides **138** and **139** effected by sodium iodide in acetone may be described as a pseudo-epoxide migration, and yields a mixture of both in the 3:1 ratio, reportedly via the 3-deoxy-3-iodo intermediate **179**.⁵²²

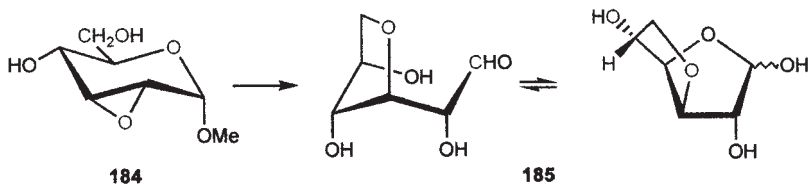


2. Interconversion of the Oxirane Ring into the Oxetane, Oxolane, and Oxane Rings

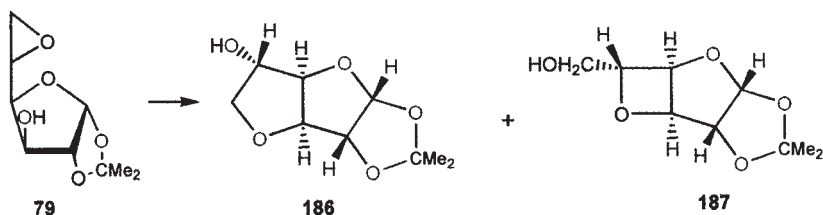
It was shown that methyl 2,3-anhydro- β -D-ribofuranoside (**180**) forms an equilibrium mixture with methyl 3,5-anhydro- β -D-xylofuranoside (**181**), whereas the corresponding α anomer **182** gives in sodium methoxide solution the major product of epoxide-ring opening, namely methyl 2-O-methyl- α -D-arabinofuranoside (**183**).^{523,524}



Acid hydrolysis of 2,3-anhydrohexopyranosides yields free 3,6-anhydrohexoses (for example, **184** \rightarrow **185**), which suggests that the hydrolysis of the glycoside bond precedes the formation of the oxolane ring.^{525,526}



Treatment of 5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose (**78**) with alkali gives 3,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose (**117**). On the other hand, the corresponding 5,6-anhydride **79** of *L*-ido-configuration yields a mixture of 3,6-anhydro-1,2-*O*-isopropylidene- α -L-idofuranose (**186**) and 3,5-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose (**187**).⁵²⁷ Inspection of molecular models clearly indicates the possibility of preferential attack of the oxirane ring at position C-5 with the OH-3 for the *ido* and not for the *gluco* configuration.



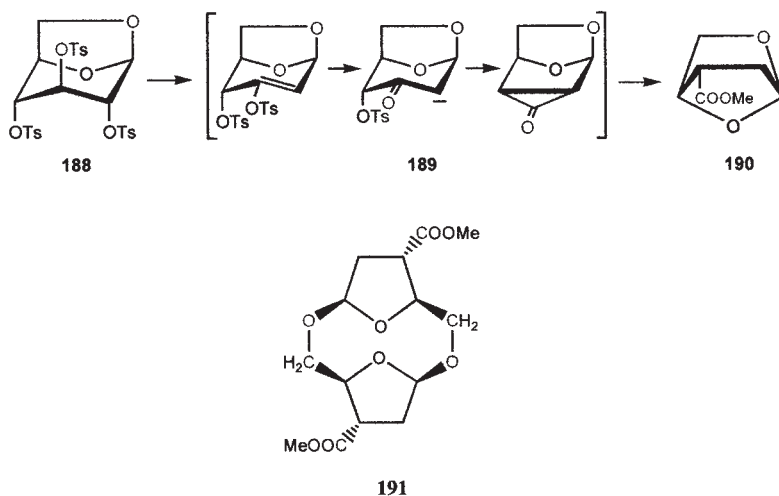
1,2-Anhydroaldohexopyranoses show a tendency for conversion into 1,6-anhydrohexopyranoses if a free hydroxymethyl group is present at C-5 and the oxirane ring adopts the appropriate *trans* orientation, see Section II.1.

3. Miscellaneous Rearrangements

Acetalation of 1,6-anhydro- β -D-mannopyranose (**39**) and - β -D-galactopyranose with trichloroacetaldehyde in the presence of *N,N'*-dicyclohexylcarbodiimide affords *endo*-H diastereomers of 3,4- and 2,3-trichloroethylidene derivatives of 1,6-anhydro- β -D-altro- and - β -D-gulopyranose, respectively.⁵²⁸ For isomerization of various 1,6-anhydrohexopyranoses acetates, see Section II.4.

A rather unique Favorskii-like rearrangement of levoglucosan tritosylate (**188**) was effected by means of sodium methoxide in methanol to afford the

branched 1,4-anhydro-2-deoxy- α -D-*erythro*-pentopyranose derivative **190** via anticipated intermediates **189**. Compound **190** undergoes cyclodimerization (and also oligomerization) in chloroform solution or during silica-gel chromatography to give the corresponding cyclic diacetal **191**.⁵²⁹



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ACIDS AND OTHER PRODUCTS OF OXIDATION OF SUGARS*

BY ROSA M. DE LEDERKREMER AND CARLA MARINO

CIHIDECAR, Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires. Pabellón II, Ciudad Universitaria, 1428 Buenos Aires, Argentina

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I. INTRODUCTION

This chapter deals with the low-molecular weight carbohydrates that can be formally considered as oxidation products of mono- or oligo-saccharides in which an aldehyde group and/or one or more hydroxyl groups have been oxidized to carbonyl and/or carboxyl groups. Some acids are important

*This chapter and the following chapter by Varela constitute an integrated overview of the products formed by oxidation of carbohydrates and the reactions involved. The subject of this contribution is structured along lines similar to the article by Theander in the 1980 second edition of "The Carbohydrates, Chemistry and Biochemistry," edited by W. Pigman and D. Horton. It includes key early references, but deals for the most part with work published after 1980. The original article by Theander¹ remains a key resource for additional detail on earlier developments.

natural products, for instance, L-ascorbic acid (vitamin C); others, such as the glycuronic acids, are constituents of abundant polysaccharides. Examples of commercial importance are: ascorbic acid, as one of the major water-soluble antioxidants; salts of gluconic acid, for instance the magnesium salt used in the pharmaceutical industry, and D-ribono-1,4-lactone, a versatile material in the synthesis of natural products.

The oxidation products are divided into two principal categories, namely, acids (and lactones) and neutral compounds.

II. ACIDS

Three kinds of sugar acids can be formally obtained from the corresponding aldoses. They are: aldonic acids, produced by oxidation at C-1 of the aldose; uronic acids, formed by oxidation of the primary alcohol group of the aldose; and aldarcic acids, formed by oxidation of both the aldehyde and the primary alcohol group.



Aldonic acids



Glycuronic acids



Aldarcic acids

Aldonic and aldarcic acids are usually obtained by oxidation methods from the corresponding aldoses, whereas a glycoside is the usual starting material for the synthesis of glycuronic acids, important natural sugars that are constituents of many polysaccharides.

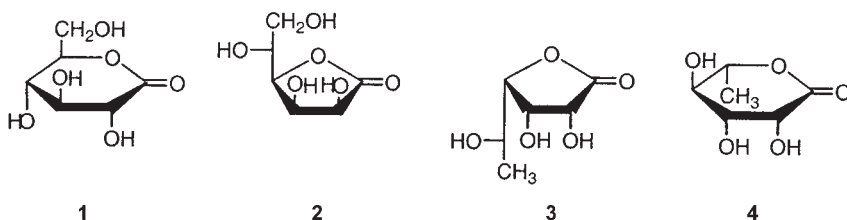
Physical constants for the acids and derivatives published prior to 1964 have been tabulated.²

1. Aldonic Acids

a. Preparation.—The methods most frequently used include: oxidation of the parent aldose; synthesis from lower aldoses; degradative oxidation of aldoses; epimerization of other aldonic acids; and various other methods.

(i) Oxidation of Aldoses.—The most widely used chemical method for preparing aldonic acids is the oxidation of the unprotected aldose with bromine in aqueous solution. The hydrobromic acid formed as a byproduct lowers the rate of oxidation; this effect is, however, minimized in buffered

solutions (pH 5–6), and for this purpose the addition of barium carbonate or barium benzoate is convenient.³ The aldonic acid is usually isolated as the lactone. D-Glucose gives the stable D-glucono-1,5-lactone (**1**),⁴ whereas under similar conditions D-mannose gives D-mannono-1,4-lactone (**2**),⁵ and L-rhamnose yields a mixture of the 1,4- and 1,5-lactones (**3** and **4**) in 1:2 ratio. The 1,5-lactone **4** can be separated by crystallization. Conversion of **4** into the more stable 1,4-lactone **3** is achieved in aqueous trifluoroacetic acid.⁶

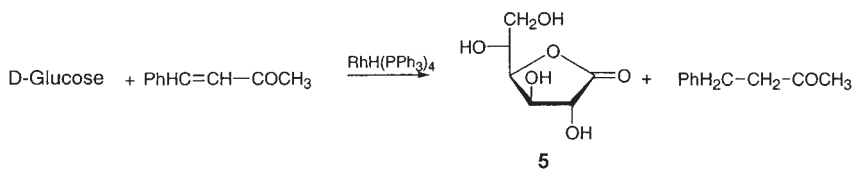


Oxidation of aldoses by hypiodite can also be used for preparative purposes.⁷ Other types of halogen oxidants, especially *N*-halo compounds, are useful. For example, *N*-bromocarbamide was recommended by Kiss⁸ as a selective and convenient reagent for oxidizing benzylated sugars to their corresponding aldonolactones in yields exceeding 90%. Another example is the use of *N*-iodosuccinimide and tetrabutylammonium iodide.⁹

Oxidation of aldoses can be achieved with other oxidants. The increased use of D-ribonolactone as a chiral intermediate in organic synthesis^{10,11} has encouraged the search for new oxidants.

Molecular oxygen in the presence of Pd/C catalyst and one equivalent of Mg(OH)₂ affords the pentonolactones with >90% yield¹² and is a useful method for the production of multigram quantities of D-ribono-1,4-lactone. Other noble metal catalysts have been used,^{11,13} some of them activated with other metals, such as gold or bismuth,¹⁴ as detailed in the following Chapter, by Varela, along with the kinetic studies performed.

The system RhH(PPh₃)₄–4-phenyl-3-buten-2-one (benzalacetone) has been applied to free and partially protected sugars to afford high yields of the 1,4-lactone.¹³ This is particularly interesting in the case of the oxidation of D-glucose, which by bromine oxidation affords the 1,5-lactone **1**.⁴ With RhH(PPh₃)₄–benzalacetone, D-glucono-1,4-lactone (**5**) was obtained in 90% yield (Scheme 1) and 2-acetamido-2-deoxy-D-glucopyranose afforded the 1,4-lactone in 62% yield. On the other hand, oxidation of 2-acetamido-2-deoxy-D-glucopyranose with aqueous bromine afforded



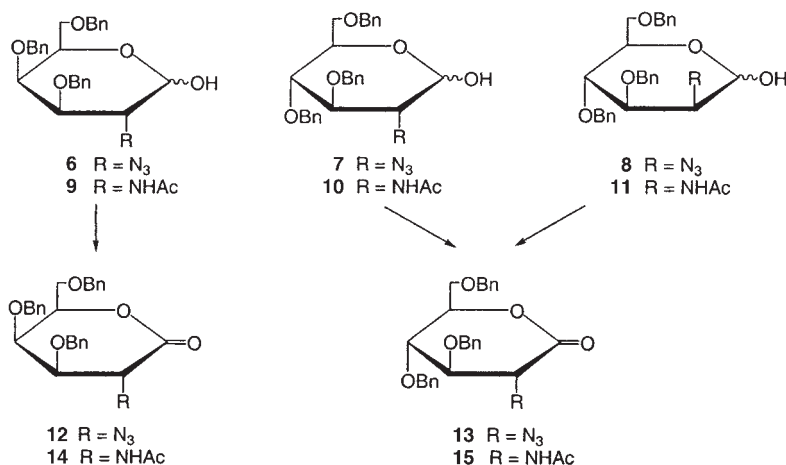
SCHEME 1

a complex mixture, from which 2-amino-2-deoxy-D-gluconic acid and 2-acetamido-2-deoxy-D-glucono-1,5-lactone were obtained in low yield.¹⁵

Many electrochemical methods for the oxidation of sugars have been developed. Conversions may be achieved by direct electron transfer between the electrode and the substrate, or by indirect electrolysis, whereby the electrons are transferred by an electrocatalyst mediator. This mediator may be one of the oxidizing agents already described, with the advantage that only a catalytic amount of oxidant is necessary since it is regenerated by the electrodic oxidation. Indirect electrolysis can lead to better selectivity because of the specific interaction of the mediator with the substrate. However, low turnovers and the need to separate the mediator from the product are possible disadvantages.¹⁶ Isbell and co-workers first developed this methodology, in which bromine is generated by the oxidation of catalytic amounts of calcium bromide in a solution containing the sugar and calcium carbonate.¹⁷ This procedure has also been adapted to a convenient laboratory-scale preparation of aldonates of mono- and di-saccharides. It was shown that oxidation by chlorine is partly a radical and partly an ionic process. When the former is retarded by chlorine dioxide, the main products from oxidation of methyl β -D-glucopyranoside are D-gluconic and D-arabinonic acids.¹⁸ A continuous method for oxidation of lactose to lactobionate has also been described, using sodium bromide as electrolyte.¹⁹

Another alternative is the autoredox reaction. D-Gluconic acid and D-glucitol were obtained concurrently in 90% yield by paired electrolysis of glucose with a lead sheet cathode and a dimensionally stable anode in a press-filtration diaphragm cell.²⁰

Other methods have been reported for the oxidation of protected aldoses at C-1. Dimethyl sulfoxide-acetic anhydride has been used for the preparation of 2-azido-2-deoxy- and 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-D-hexono-1,5-lactones from the corresponding lactols. Derivatives having the D-galacto (**6** and **9**) and D-gluco (**7** and **10**) configurations gave the corresponding lactones in very good yields ($\sim 90\%$), whereas the D-mannopyranose derivatives (**8** and **11**) afforded the substituted D-gluconolactone



SCHEME 2

derivatives **13** and **15** (92%), with complete epimerization at C-2 (Scheme 2). The 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galacto- (**9**) and -glucopyranoses (**10**), when oxidized with tetra-*N*-propylammonium tetraoxoruthenate in the presence of 4-methylmorpholine-*N*-oxide afforded the corresponding lactones in 90% yield. The D-manno derivative (**11**) was likewise epimerized at C-2 to give the D-gluconolactone derivative (**15**).²¹ Tetra-*n*-propylammonium tetraoxoruthenate(VII) (TPAP) has been used for the oxidation of protected glycopyranoses and glycofuranoses. The pure lactones were obtained in >80% yield.²²

Oxidation of 2,3-*O*-cyclohexylidene-D-ribose by pyridinium chlorochromate gave 2,3-*O*-cyclohexylidene-D-ribonono-1,4-lactone in 55–60% yield.²³

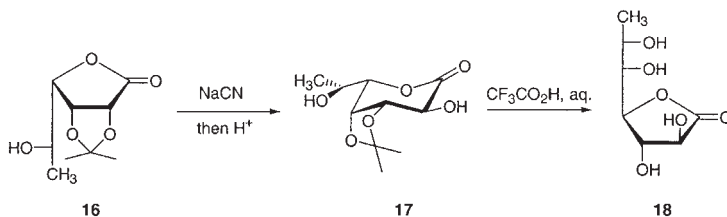
Photochemical procedures have also been reported. For instance, some phenacyl glycosides undergo a Norrish type II photochemical reaction to give lactones on photolysis with pyrex-filtered UV light.²⁴

Oxidation of aldoses with microorganisms or with purified enzymes has been described (see also the following Chapter). Aldonic acids can be produced in good yield by many species of bacteria and molds. Thus, calcium D-gluconate was obtained in >90% from a *Micrococcus* species grown on acetate as the sole carbon source.²⁵ Lactose undergoes stoichiometric oxidation to lactobionic acid by *Pseudomonas graveolens*,²⁶ and gluconic and galactonic acids have been obtained from lactose in ultrafiltrates of whey by microbiological hydrolysis and oxidation.²⁷

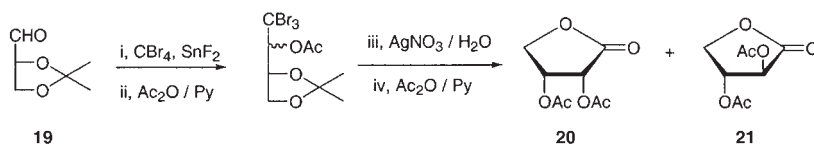
The purified enzyme D-glucose oxidase (EC 1.1.3.4) has also been used for the selective oxidation of β -D-glucopyranose to D-glucono-1,4-lactone. This reaction is used in a sensitive test to determine glucose.²⁸ Immobilized glucose oxidase-catalase has been used for the oxidation of D-glucose to D-gluconic acid.²⁹ Another enzyme used for the oxidation is D-glucose-phosphate dehydrogenase.³⁰

(ii) **Synthesis from Lower Aldoses.**—Aldonic acids may be prepared from an aldose having one fewer carbon atom by the Kiliani cyanohydrin synthesis. A new asymmetric center is created and the ratio of epimers depends on the conditions under which the reaction of the aldose with cyanide takes place.³¹ Many methods have been used for separating the two epimeric acids formed. In the form of lactones or esters, they can be reduced to aldoses. The first methods used sodium amalgam in mild acid solution for reduction of the lactone.³² The Kiliani method has been used for the synthesis of [¹⁴C]-labeled acids and aldoses, using ¹⁴C-labeled sodium cyanide. Thus, starting from arabinose, and Na¹⁴CN, D-[1-¹⁴C] glucose and D-[1-¹⁴C] mannose were synthesized.³³ (1-¹³C)aldono-1,4-lactones have also been synthesized for studies of solution conformations deduced from NMR data.^{34,35}

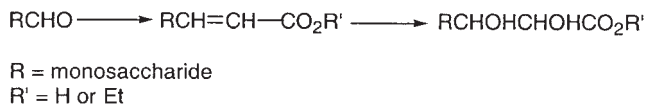
The Kiliani reaction has also been applied to substituted aldoses. The substituted lactones obtained may be reduced efficiently to the aldoses with diisooamylborane.^{36,37} Thus, in a large-scale reaction,³⁸ di-*O*-isopropylidene-D-mannofuranose gave D-*glycero*-D-*talo*-heptonolactone and its D-*glycero*-D-galacto isomer in 2.5:1 ratio. Treatment of the L-rhamnose derivative **16** under Kiliani conditions gave a 3:1 preponderance of the D-*glycero*-L-*galacto*-lactone **17** over the C-2 epimer. Reaction of **17** with aqueous trifluoroacetic acid gave the 1,4-lactone **18**, convertible into its 5,6-*O*-isopropylidene derivative.³⁹



Reaction of aldehydes with carbon tetrabromide and tin(II) fluoride gives adducts, formed by addition of the elements of bromoform across the carbonyl group, which may be hydrolyzed to acids. In this way, 2,3-*O*-isopropylidene-D-glyceraldehyde (**19**) was converted into a mixture of D-*erythro* (**20**) and D-*threo*-tetronolactones (**21**).⁴⁰

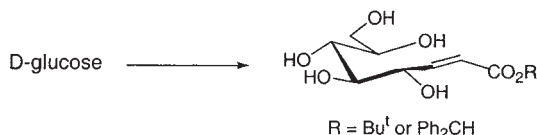


A general method involving elongation of the carbon chain by two carbon atoms has been developed by Kochetkov and Dmitriev; it is based on the transformation of an *aldehydo*-aldose into the homologous *trans*-2,3-dideoxyald-2-enonic acid or its ester, and subsequent hydroxylation of the double bond to afford the two diastereoisomeric aldonic acids having the *D-threo* and *L-threo* stereochemistry, respectively, at the newly created asymmetric centers, and the same configuration as the original aldose in the rest of the molecule (Scheme 3).



SCHEME 3

Many examples of preparations of heptonic and octonic acids in good yields have been reported. The chain-extension step is the condensation of the protected aldehydo derivative with malonic acid (Knoevenagel–Doebner condensation) or with (ethoxycarbonylmethylene)triphenylphosphorane (Wittig reaction), followed by hydroxylation with osmium tetroxide in the presence of a suitable oxidant; the optimal oxidant differs for various types of unsaturated intermediates.⁴¹ An application of the Wittig chain extension of unprotected aldoses (using $\text{Ph}_3\text{P}=\text{CHCO}_2\text{R}$, and bulky R groups Bu^t , Ph_2CH), gave good yields of the acyclic α,β -unsaturated esters, with the *E* isomers the predominant products.⁴² An example is shown in Scheme 4.

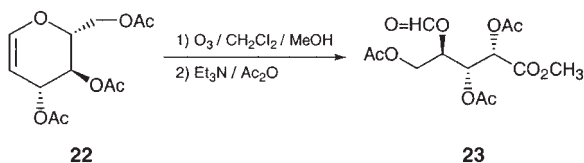


SCHEME 4

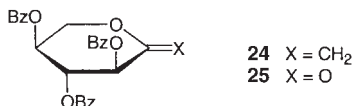
(iii) Degradative Oxidation of Aldoses.—Controlled, degradative, alkaline oxidation of aldoses affords aldonic acids containing one fewer carbon atom. Spengler and Pfannenstiel oxidized D-fructose or D-glucose with oxygen in alkaline solution to give sodium D-arabinonate in 70% yield.⁴³ By the same method, D-ribose and L-arabinose have been degraded to D- and

L-erythronic acids, respectively, and D-xylose to D-threonic acid.⁴⁴ Isbell *et al.* elucidated the mechanism of this process⁴⁵ (see the following Chapter). Degradation to a lower aldonic acid can be achieved by oxidation of an unsaturated sugar derivative. The method of Reichstein *et al.*⁴⁶ for the preparation of L-threono-1,4-lactone by permanganate oxidation of 5,6-*O*-isopropylidene-L-ascorbic acid was improved by Perel and Dayton to afford the crystalline lactone in 65% yield.⁴⁷

Ozonolysis of tri-*O*-acetyl-D-glucal (**22**) followed by work-up with Et₃N–Ac₂O, led to the *O*-formylated derivative **23** of methyl-D-arabinonate in 77% yield.⁴⁸

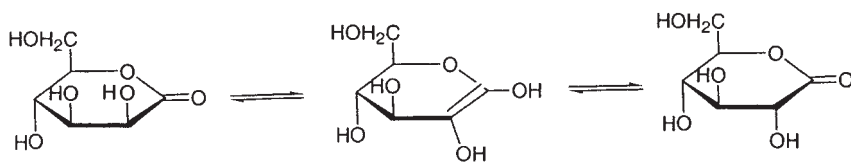


Ozonolysis of the methylene sugar derivative **24**, derived from L-sorbose, afforded L-xylic-1,5-lactone **25**.⁴⁹



(iv) Epimerization of Other Aldonic Acids.—By alkaline treatment and heating, the aldonic acids undergo epimerization at C-2 (see Section II.1.b). An example is the classical epimerization of D-mannonic acid performed by Emil Fischer in 1890.⁵⁰ A mixture of D-gluconic and D-mannonic acid was prepared by heating a solution of the latter in pyridine. This method is of interest for the production of D-ribonic acid from D-arabinonic acid by epimerization in pyridine or other media. The D-arabinonic acid used can be prepared from D-glucose by oxidative degradation. Potassium arabinonate can be epimerized at 130–140 °C for 4 h and the resulting ribonate is crystallized as the ribonolactone after purification by passing over a cation-exchange resin.⁵¹

Epimerization may also occur when the hydroxyl group at C-2 is methylated; thus the tetra-*O*-methyl derivatives of both D-glucono-1,4- and 1,5-lactones may be converted into the corresponding tetra-*O*-methyl-D-mannonolactones. The epimerization may take place, as with the sugars, through an intermediate enediol (Scheme 5); this mechanism also accounts for the reaction of methylated derivatives, as the methoxyl group at C-2 is present merely as a substituent. Later investigations showed⁵² that

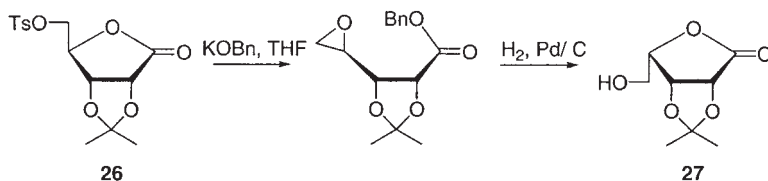


SCHEME 5

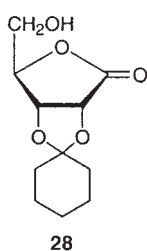
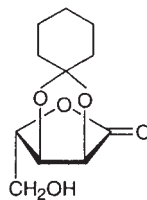
marked epimerization of aldonic acids also occurs in water at pH 7–8 and 60–100 °C.

Epimerization of the potassium salts of L-arabinonic, D-ribonic, D-lyxonic, and D-xylonic acids in aqueous alkali was monitored kinetically by gas-chromatographic analysis of the silylated samples. Mass-spectrometric measurements indicated⁵³ that the reaction proceeded by complete proton exchange at C-2.

Epimerization at positions other than C-2 may afford additional aldonic products. Thus, the D-ribonolactone derivative **26** was efficiently epimerized to the lyxonolactone **27**.⁵⁴



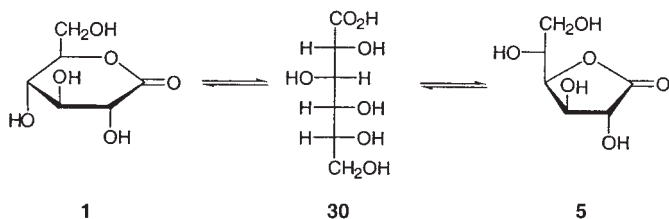
Interestingly, the ribonolactone acetal (**28**) was converted into its enantiomer (**29**) by interconversion of the oxidation levels at C-1 and C-5 followed by an acetal-migration step.⁵⁵

**28****29**

(v) *Other Methods*.—Bestmann and Schmiechen synthesized L-threono-1,4-lactone from L-threonic acid via reduction of methyl 2,3-di-O-acetyl-L-threonyl chloride.⁵⁶

Hydrogenation of L-ascorbic acid (Rh/C, H₂) afforded L-gulono-1,4-lactone.⁵⁷

b. Properties and Reactions.—(i) Lactonization.—Aqueous solutions of aldonic acids undergo equilibration between the acid and lactone forms if this is not prevented by substitution. For example, the carboxyl group of D-gluconic acid (**30**) may lactonize by condensation with the hydroxyl group on C-4 or C-5 to generate the 1,4-(γ , **5**) or 1,5-(δ , **1**) lactones, respectively; the proportion of acid and lactones depends on the configuration of the asymmetric carbon atoms. There is a significant difference in the reactivity of the two types of lactones. The 1,5-lactones are usually hydrolyzed readily and may exhibit rapid mutarotation in aqueous solution, whereas the 1,4-lactones are more stable. This is also true for the methylated lactones.⁵⁸



The rates of hydrolysis of the lactones depend on the parent structure; for instance, the 1,4-lactone of D-mannonic acid is more stable than that of D-gluconic acid, and the 1,4-lactones of 2-deoxyaldonic acids are more stable than the corresponding aldolactones. The final attainment of equilibrium between free aldonic acids and their lactones is reached only after many days at room temperature; it is, however, accelerated by the presence of strong acids and by heating. A detailed discussion of the formation and hydrolysis of aldolactones is available in a review by Shafizadeh,⁵⁹ and the conformations and stabilities of aldolactones have been discussed by Lemieux.⁶⁰ Detailed analyses of D-glucono-1,5-lactone and other lactones have been reported.⁶¹ ¹³C NMR spectroscopy proved to be a convenient method for monitoring the equilibria.⁶²

The equilibrium proportions of the constituents vary with temperature, concentration, and solvent, and are characteristic of each individual aldonic acid. Dehydration *in vacuo*, or by evaporation from suitable solvents, promotes lactone formation. By suitable choice of conditions, many aldonic acids and both types of lactones have been obtained crystalline;¹ considerations have been detailed by Isbell and Frush.⁶³

On paper or TLC chromatograms, the equilibrium mixture of acid and lactones often gives a slow-moving, elongated spot for the acid and one or two faster-moving spots corresponding to the lactones. On electrophoretograms, a nonmigrating spot appears for the lactones, whereas the spot for the acid migrates. The lactones give a violet coloration when the paper is treated with the hydroxamic reagent.⁶⁴

The relationship between structure and paper-chromatographic mobility of aldono-1,4-lactones has been discussed.⁶⁵ Butanone, saturated with water, is suitable for the preparative separation of lactones on cellulose columns; free acids and reducing sugars move very slowly in this system. Separation of aldono-1,4-lactones and of aldonic acids as their *O*-(trimethylsilyl) derivatives has been accomplished.⁶⁶ The mass spectra of such derivatives are characteristic, so that it is possible to identify aldonic acids⁶⁷ and lactones⁶⁸ by means of combined gas chromatography-mass spectrometry.

Under dehydrating conditions, it is probable that, in addition to lactonization, intermolecular esterification also occurs, yielding esters of aldonic acids and polymers.

The carbonyl frequency in the infrared spectrum provides a fairly characteristic method for differentiating between 1,4- and 1,5-lactones of aldonic acids. With few exceptions, the absorptions are in the range 1790–1765 and 1760 to 1725 cm^{-1} , respectively.⁶⁹ Configurational and conformational conclusions have been drawn from ^1H and ^{13}C NMR spectroscopy of aldonic acids and aldonolactones, using different correlation methods, enriched compounds, and shift reagents. For example, the solution conformation of aldono-1,4-lactones enriched with ^{13}C at C-1 have been determined on the basis of the coupling constants (homo and heteronuclear). In general, O-2 is oriented quasi-equatorially due to stereoelectronic factors.³⁶ Similar conclusions were made by Horton and Walaszek, who described the conformation of pentono-1,4-lactones as an equilibrium between the 3E and E_3 forms.⁷⁰ Conformations of D-hexono-1,4-lactones in solution have also been studied by NMR spectroscopy.^{70a} The solution equilibrium of protected derivatives and their conformations have been described.⁷¹

(ii) Optical Rotatory Relationships.—A number of empirical relationships have been derived from the optical rotations of acids, lactones, salts, and various derivatives. These relationships have been important in establishing the configurations of new acids, in particular of the epimers produced in the cyanohydrin synthesis. They have also been useful in establishing the ring size of lactones.

Because of the conformational restraints imposed by ring formation, the lactones have considerably higher magnitudes of rotation than the free acids. Hudson⁷² correlated the optical rotations of a number of lactones and found that the configurations of the hydroxyl groups on C-4 and C-5 exert a profound influence on the rotations. His "lactone rule" stipulates that a lactone is more dextrorotatory than the corresponding free acid if the hydroxyl group involved in lactone formation lies on the right-hand side in the Fischer projection formula; conversely, the lactone is more levorotatory if the hydroxyl group is on the left side. Thus, 1,4- and 1,5-lactones of both D-gluconic and D-mannonic acids are dextrorotatory, whereas D-galactonic and D-gulonic acids form levorotatory 1,4-lactones and dextrorotatory 1,5-lactones.

The rotations of acyclic derivatives of the aldonic acids are influenced most strongly by the configuration of the adjacent carbon atom (C-2). Those amides⁷³ in which the hydroxyl group at C-2 lies to the right in the Fischer formula are dextrorotatory; for example, the amide of D-gluconic acid has $[\alpha]_D + 31^\circ$, whereas the amide of D-mannonic acid is levorotatory, $[\alpha]_D - 17^\circ$. A similar rule also applies for phenylhydrazides⁷⁴ and benzimidazoles.⁷⁵ More details about these and related rules, with a discussion of exceptions and supplementations, are found in Ref. 1 and in a review by Klyne.⁷⁶

Optical rotatory dispersion studies on lactones of aldonic acids and other carbohydrate acids were made by Hirst *et al.*⁷⁷ and later by Okuda *et al.*⁷⁸ The latter workers related the absolute configuration at C-2 of aldono-1,4-lactones to the sign of the Cotton effect.

(iii) Other Properties and Reactions.—Aldonic acids have the general properties of carboxylic acids, and their aqueous solutions have a pH of 2–3. They form salts, some of which are sparingly soluble (for example, lead and cadmium salts), and these can be used for separation of epimeric acids. The lactones (in particular the 1,4-lactones) require an excess of alkali or elevated temperatures for conversion into salts in a reasonable period of time. Aldonic acids and lactones are stable toward acids. However, in alkaline solution, or by heating, the configuration at C-2 of aldonic acids can be altered (see Section II.1a(iv)).

Two useful preparations of lower sugars by degradation of aldonic acids are discussed in the following Chapter. These are the traditional oxidation of salts of aldonic acids with hydrogen peroxide in the presence of ferric acetate (Ruff degradation) and the related oxidation of aldonic acids by hypochlorite, which was developed by Whistler and Schweiger.⁷⁹

Aldonic acids form crystalline esters, amides, hydrazides, and benzimidazoles. Many of these derivatives, as well as the lactones, have been valuable

in the characterization and identification not only of aldonic acids but also of sugars and methyl ethers after their conversion into aldonic acids.

Esters are prepared by reaction of aldonic acids or lactones with an alcohol in the presence of hydrogen chloride;⁸⁰ the reaction is slower with 1,4-lactones. Amides are readily formed from lactones by reaction with liquid ammonia followed by evaporation of the solvent.⁸¹ D-Gluconamide has also been prepared by treatment of D-glucono-1,5-lactone with concentrated ammonium hydroxide and subsequent precipitation with ethanol.⁸² N-Substituted aldonamides may be obtained by reaction of the aldonolactones with ethanolamine, diethanolamine, and related species.⁸³

Aldonamides having five or more carbon atoms in the sugar chain are hydrolyzed in aqueous solution with accompanying mutarotation⁸⁴ but those of tetrionic acids are, however, stable.⁸⁵ Lower sugars may be prepared from aldonamides by the Weerman degradation method.

Fully acetylated aldonic acids can be prepared by oxidation of *aldehydo*-sugar peracetates. Direct acetylation of certain aldonic acid salts is possible, and addition of cadmium salts, in particular, affords high yields of acetates. The synthesis can also be accomplished by deamination of the readily prepared, acetylated amides with nitrous acid or nitrosyl chloride. Examples of the various methods are given in Ref. 86.

Fully acetylated aldonyl chlorides have been prepared by treatment of acetylated aldonic acids with phosphorus pentachloride⁸⁷ or thionyl chloride.⁸⁸ Dichloromethyl methyl ether was later shown to afford the derivative of D-gluconic acid in almost quantitative yield.⁸⁹

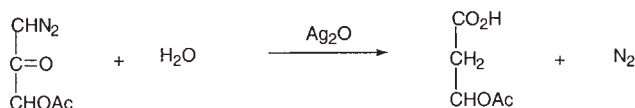
Bognar and co-workers prepared a series of acetylated aldonic acid chlorides⁹⁰ and bromides⁹¹ by the action of dihalomethyl methyl ethers and other reagents. Crystalline azides, "anilides," and "4-aminosulfonyl-anilides" were prepared from the acetylated aldonyl chlorides in good yields; crystalline products also resulted on saponification of the acyl protecting groups.

Acetylated aldonyl chlorides⁹² and thioesters⁹³ can be reduced catalytically to open-chain derivatives of aldoses.

The action of diazomethane converts acetylated aldonyl chlorides into 1-diazoketose derivatives having one additional carbon atom in the carbon chain; the diazo group may be replaced by different nucleophiles. This versatile synthesis of ketoses has been widely applied by Wolfrom and Thompson.⁹⁴

Treatment with silver oxide in water causes these α -diazoketones to undergo the Wolff rearrangement, yielding 2-deoxyaldonic acids (Scheme 6).⁹⁵

The use of aldonolactones in synthesis has been extensively reviewed, concerning among other topics *O*-substitution, deoxygenation, reaction with



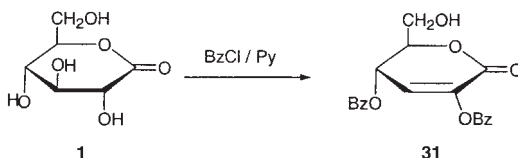
SCHEME 6

nucleophiles, β -elimination, and the use of aldono-lactones in preparing other classes of compounds such as iminoalditols.³⁷ Aldono-lactones have been widely used as chiral starting compounds in the synthesis of carbohydrates and noncarbohydrate natural products.^{11,96}

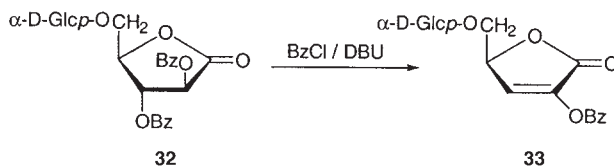
The use of partially protected aldono-1,4-lactones as glycosyl acceptors led to glycosylaldono-1,4-lactones, which are useful precursors of disaccharides containing furanoid reducing units.⁹⁷

Heptonolactones, in which all the functional groups except one can be protected, also offer great potential as starting materials in synthesis.³⁸

The acylation of aldono-lactones over extended periods leads to the formation of unsaturated lactones, with β -elimination being promoted by pyridine. Thus, treatment of D-glucono-1,5-lactone with an excess of benzoyl chloride and pyridine for 16 h at room temperature gave crystalline 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**31**) in 97% yield.⁹⁸ Other examples may be found in Ref. 37.



Other basic reagents cause the same effect. Thus, 2,3,4-tri-*O*-methylpentono-lactones when treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) generate the 3-deoxy-2,3-unsaturated products, which on hydrogenation selectively afford 3-deoxy-2,4-di-*O*-methyl-D- or L-*erythro*-pentono-lactones. The selectivity of the hydrogenation is governed by the stereochemistry at C-4.⁹⁹ Similar β -elimination can be performed with glycosyl aldono-lactones. Thus, the 1,4-lactone **32** gave the 3-deoxy-2-ene derivative **33** by benzylation and treatment with DBU.¹⁰⁰

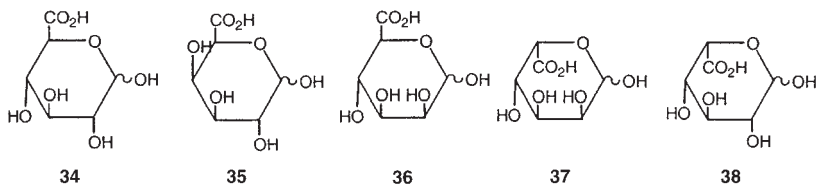


The β -elimination reaction has been used as the first step for the enantioselective synthesis of 1,3-polyols, starting from per-*O*-benzoyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone.¹⁰¹

From 7-bromo-7-deoxy-D-*galacto*-heptono-1,4-lactone, highly functionalized cyclopentanes have been prepared.¹⁰² Other reactions of aldono-lactones are discussed in Ref. 37.

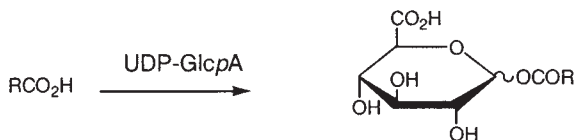
2. Glycuronic Acids

The glycuronic acids may be regarded as aldoses in which the primary alcoholic group has been oxidized to a carboxyl group or, alternatively, as aldso- ω -onic acids. As with aldoses, they can exist in both furanose and pyranose forms, and, like aldonic acids, they can lactonize. The structures of naturally occurring examples are here depicted in the pyranose forms: D-glucuronic acid (**34**), D-galacturonic acid (**35**), D-mannuronic acid (**36**), L-guluronic acid (**37**), and L-iduronic acid (**38**).



a. Occurrence.—The uronic acids occur naturally in combined form, mainly as constituents of polysaccharides. In particular, D-glucuronic acid (**34**) is also present in metabolic products of low molecular weight. It serves as a detoxifying agent in mammals, and some poisonous compounds are excreted in the urine and bile as alkyl or aryl D-glucosiduronic acids.^{103–105} The acid was first isolated from such a conjugate by Jaffé in 1878, and was prepared for many years by feeding borneol or menthol to animals. It was also established that the 6- β -D-glucopyranosyluronic acid derivative of morphine is a metabolite of morphine, and it has greater analgesic activity than morphine itself.¹⁰⁶ Many acidic drugs, such as the nonsteroidal antiinflammatory drugs, are metabolized in the liver to form unstable 1-*O*-acyl- β -D-glucuronic acids, which are excreted (Scheme 7).¹⁰⁷

Animal polysaccharides containing D-glucuronic acid include heparan sulfate,¹⁰⁸ chondroitin 4- and 6-sulfates,¹⁰⁹ and hyaluronic acid.¹⁰⁹



SCHEME 7

Among the plant polysaccharides there may be mentioned the hemicelluloses; the most common of these contain 4-*O*-methyl-D-glucuronic acid as branch units linked to a β -D-xylan backbone.¹¹⁰ The commercially important gum arabic, a soluble polysaccharide produced by *Acacia* trees and widely used in foods and pharmaceuticals, also contains glucuronic units.¹¹¹ D-Glucuronic acid has been found in sulfated complex polysaccharides from brown algae.¹¹²

The acid also occurs in many flavonol glycosides of plants, and α -linked to a glycerol unit, it has been found as a constituent of ardisicrenoside E, a triterpenoid pentasaccharide from *Ardisia crenata*.¹¹³

D-Glucuronic acid is a component of many bacterial polysaccharides, thus it is part of the repeating pentasaccharide containing two D-glucose and two D-mannose units in xanthan, a commercially important extracellular polysaccharide produced by *Xanthomonas* sp.¹¹⁴ Certain bacteria elaborate gels having physical characteristics similar to seaweed gels. Thus, gellan, produced by *Pseudomonas elodea*, is a polysaccharide having a tetrasaccharide repeating-sequence containing β -D-glucopyranosyluronic acid.¹¹⁵⁻¹¹⁷ Similar polysaccharides include welan¹¹⁸ and rhamsan, produced by *Alcaligenes* sp.¹¹⁹

Glucuronic acid is also constituent of pathogenic bacteria. The simplest structure for a pneumococcal capsular polysaccharide has the repeating unit $[\rightarrow 4)\text{-}\beta\text{-D-Glc-(1}\rightarrow 3)\text{-}\beta\text{-D-GlcA-(1}\rightarrow]_n$.¹²⁰

Microbial polysaccharides may contain substituted glucuronic acids. 4-*O*-(L-1-Carboxyethyl)-D-glucuronic acid has been identified¹²¹ as component of the capsular polysaccharide from *Klebsiella* type 37, and 3-*O*-(L-1-carboxyethyl)-D-glucuronic acid has been found in the exopolysaccharide produced by *Altermonas* sp. 1644.¹²²

D-Galacturonic acid (35) is a common polysaccharide component in the plant kingdom. Its α -(1 \rightarrow 4)-linked polymer forms the building unit of pectins.¹²³ Some of the carboxyl groups are esterified with methanol and some units are substituted with 2-*O*- or 3-*O*-acetyl groups.

A pectic polysaccharide containing D-galacturonic acid and terminal units of 4-*O*-methyl-D-glucuronic acid, along with L-rhamnose and D-galactopyranose, was purified from yellow mustard mucilage.¹²⁴ Pectins are prevalent

in fruits, where they stabilize their shapes, and they are most commonly isolated from apples. They are used commercially in foods, mainly as gelling agents.

D-Galacturonic acid has also been found in bacterial polysaccharides.^{125,126} In several *Proteus* O-antigens, amino acids are amide-linked to the carboxyl group of α -D-galacturonic¹²⁷ or glucuronic acid.¹²⁸ It has been shown that D-galacturonic acid replaces phosphate residues in the lipid A component of the lipopolysaccharide (LPS) from the bacterium *Aquifex pyrophilus*.¹²⁹

D-Mannuronic acid (36) constitutes the major component of alginic acid, the main polysaccharide of the brown algae, in which L-guluronic acid (37) is also found. The ratio of D-mannuronic acid and L-guluronic acid can vary with the algal species, the type of tissue, and the age of the plant. In the case of *Laminaria hyperborea*, L-guluronic acid is the major component.¹³⁰

Algins rich in mannuronic acid can be biosynthesized by bacteria.¹³¹⁻¹³⁴ With divalent metal ions, alginates form gels that have important uses.¹³⁵

L-Iduronic acid (38) is a constituent of heparin, dermatan sulfate, and a type-specific polysaccharide of *Clostridium perfringens*.¹³⁶ A 5-epimerase acting on some animal polysaccharides causes the inversion of the carboxylate group of the D-glucuronic acid residues to give rise to α -L-iduronic acid units. Heparin, arising from heparan sulfate, contains the repeating disaccharide [$\rightarrow 4$)- α -L-idopyranosyluronic acid-(1 \rightarrow 4)-2-deoxy-2-sulfoamino-D-glucopyranose-(1 \rightarrow)]. The polysaccharide contains a variable number of sulfate groups at C-2 of the L-iduronic acid residues and at OH-6 of the D-glucosamine units.¹⁰⁸ It has important clinical application as an anticoagulant.

Dermatan sulfate, found primarily in mammalian skin, has the repeating unit [$\rightarrow 4$)- α -L-idopyranosyluronic acid-(1 \rightarrow 3)-2-acetamido-2-deoxy-4-O-sulfo- β -D-galactopyranosyl-(1 \rightarrow)]. Some of the L-iduronic acid residues are sulfated at O-2.¹⁰⁸

Aminohexuronic acids have been found in some bacterial polysaccharides, for example, 2-amino-2-deoxy-D-galacturonic acid, which was isolated from the Vi-antigen of *Escherichia coli* and other organisms.^{137,138} The presence of 2-acetamido-2-deoxy-D-mannuronic acid¹³⁹ and 2-amino-2-deoxy-D-glucuronic acid¹⁴⁰ has been demonstrated in other microbial polymers. 2-Amino-2-deoxy- α -L-altropyranosiduronic acid is present in *Shigella sonnei* phase I O-antigen.¹⁴¹ 5-Amino-5-deoxy-D-alluronic acid has been identified as the sugar moiety common to the polyoxins.¹⁴²

Penturonic acids have been also found in natural products. Thus, sitosterol 3-O- α -D-xyluronofuranoside has been isolated from

Bauhinia candicans,¹⁴³ and a sterol conjugated as a D-riburonofuranoside has been isolated from the same plant.¹⁴⁴

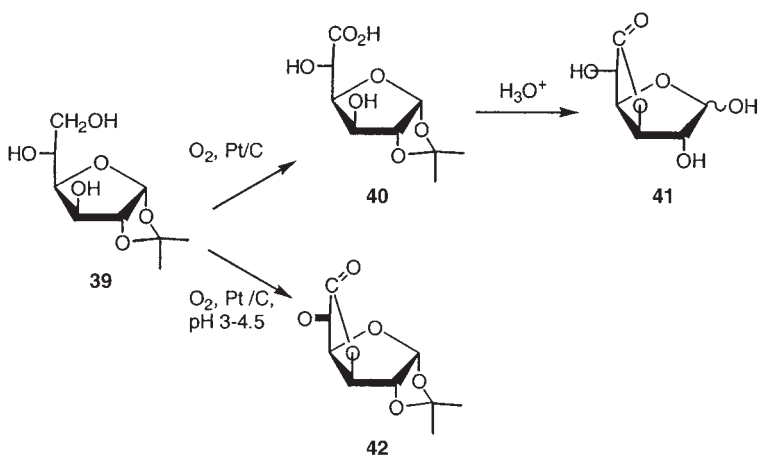
b. Preparation.—The isolation of uronic acids from polysaccharides is usually difficult, and yields of monomeric uronic acids are usually low. The reason for this is that the glycosidic linkages of uronic acids are more acid-stable than glycosidic linkages of neutral constituents, while the free uronic acids are degraded more readily than neutral sugars. The resistance of the glycosiduronic linkages to scission can sometimes be used for the identification of glycosidic linkages by separation and identification of the aldobionuronic (disaccharidic) fragments. Nevertheless, L-iduronic and D-mannuronic acids have been isolated in gram quantities as their brucine salts from the hydrolyzate of alginic acid.¹⁴⁵ Enzymic hydrolysis of pectin has been used for the isolation of D-galacturonic acid in good yield.¹⁴⁶

Methods for the chemical synthesis of glycuronic acids include: (i) reduction of the monolactones of aldaric acids, (ii) oxidation of the primary alcoholic group of aldose derivatives, (iii) oxidative degradation procedures, (iv) chain-extension reactions on dialdoses, and (v) epimerization reactions.

(i) Reduction of Monolactones of Aldaric Acids.—Although used for the first chemical synthesis of D-glucuronic acid (in low yield from D-glucaro-1,4-lactone),¹⁴⁷ the reductive approach has not been developed, owing to the difficulty of obtaining pure 1,4-lactones for reduction.

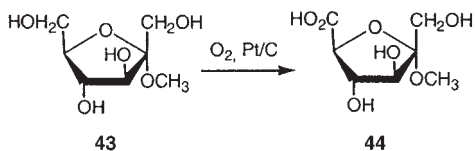
(ii) Oxidation of the Primary Alcohol Group.—These oxidative methods require protection of the aldehyde group and of the secondary hydroxyl groups, or else the use of selective oxidants. The protecting groups most commonly used have been isopropylidene acetals and acetates; the former are stable under neutral or alkaline conditions, and the latter may be employed under acidic conditions. The main interest has centered around the synthesis of D-glucuronic acid.^{148,149}

Mehlretter and co-workers prepared D-glucuronic acid by catalytic oxidation of 1,2-O-isopropylidene- α -D-glucofuranose (**39**) at pH 8–9. The intermediate 1,2-O-isopropylidene- α -D-glucofuranuronic acid (**40**), obtained in 50–60% yield, could be hydrolyzed almost quantitatively to D-glucuronic acid, which was isolated as the crystalline lactone **41**. At pH 3–4.5, oxidation of the 5-hydroxyl group also occurs, resulting in good yield of the 5-keto analogue **42**¹⁴⁹ (see Section II.2.d).

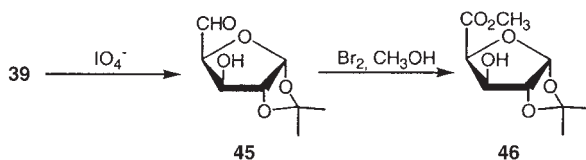


Many glycosiduronic acids have been prepared in good yield by selective catalytic oxidation of alkyl glycopyranosides. The effect of the alkyl substituent on reactivity and selectivity has been studied.¹⁵⁰

Platinum-catalyzed oxidation of methyl α -D-fructofuranoside (**43**) with oxygen is selective for C-6, and fructuronic acid (**44**) was obtained in 80% yield.¹⁵¹



Bromine in an alcohol can be used for the direct conversion of an aldehyde into an ester, as with **46**.¹⁵² The aldehyde **45** can be generated *in situ* by Swern oxidation of an alcohol or, as in the case of the diol **39**, by periodate cleavage.¹⁵³



In aqueous alkaline solution or in acetic acid, potassium permanganate is a nonspecific oxidant that has been used in the preparation of uronic acids and derivatives. Thus, good yields of D-galacturonic acid (**35**) may be obtained by oxidation of 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose.¹⁵⁴ D-Glucuronic acid (**34**) can be prepared from starch by oxidation

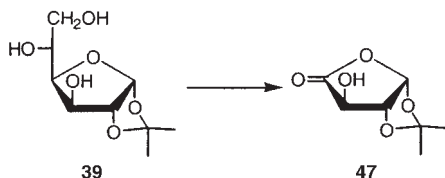
with nitric acid.¹⁰³ Other oxidative reagents for the primary hydroxymethyl group of glycosides have been used.^{155,156} Selective oxidation of the primary alcohol group of aldoses to uronic acids can be achieved by use of sodium hypochlorite in the presence of 1 mol% of 2,2,6,6-tetramethyl-1-piperidyl radical (TEMPO).¹⁵⁷ This method has also been used for the synthesis of methyl 4-*O*-methyl- α -D-glucopyranosiduronic acid.¹⁵⁸ For other references on TEMPO-mediated oxidations, see also the following chapter.

Several electrochemical oxidations have also been described for preparing glycuronic acids. A nickel hydroxide electrode in alkaline solution has been particularly useful because of its selectivity, as secondary alcohols are not affected.¹⁵⁹

Oxidation at C-6 of hexosides can also be performed by enzymic methods or by combined procedures. Oxidation of methyl α - or β -galactopyranoside to the corresponding aldehydes using galactose oxidase, followed by chemical oxidation with O_2 /Pt-C, gave high yields of methyl galactopyranosiduronates.

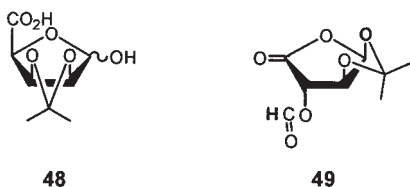
Uridine 5'-(α -D-glucopyranosyluronic acid diphosphate) (UDP-glucuronic acid) has been prepared enzymically from UDP-Glc on a gram scale by using UDP-Glc dehydrogenase.¹⁶⁰

(iii) Oxidative Degradation Procedures.—The use of potassium permanganate in conjunction with copper sulfate can effect an interesting oxidative degradation of otherwise protected furanosides having a carbonyl or alcohol function at C-5, as in the conversion of **39** to **47**.¹⁶¹

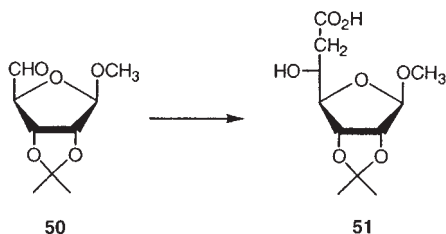


D-Lyxuronic acid results from the degradation of D-galactaric acid monoamide with hydrogen peroxide and iron salts.¹⁶² Some glycuronic acids have been prepared by glycol cleavage of higher acids. D-Glucofuranurono-6,3-lactone (**41**) was treated with an equimolar proportion of lead tetraacetate and, after hydrolysis of the resulting formic ester group, gave a good yield of D-arabinurono-5,2-lactone, together with some of the free acid. D-Galactofuranuronic acid and potassium D-glucofuranuronate have likewise been degraded to D-threuronic and D-erythruronic acids, respectively.¹⁶³ Oxidation of D-galactono-1,4-lactone by one molar equivalent of periodate affords L-lyxuronic acid, which may be isolated as methyl

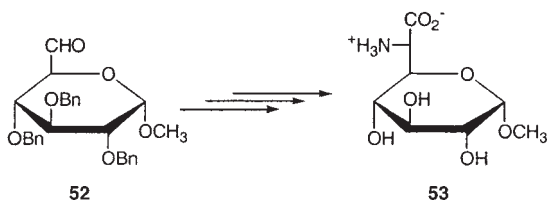
L-lyxuronate.¹⁶⁴ Aldopyranosuronic and aldofuranoseuronic acid lactones, with one fewer carbon atom, can be specifically obtained when hexuronic and penturonic acids in their pyranose or furanose forms undergo a fragmentation–cyclization reaction promoted by the system (diacetoxyiodo)benzene–iodine, under mild conditions. For example, **48** gave lactone **49** in 51% yield¹⁶⁵ and a similar reaction takes place with diphenylhydroxyselenium acetate–iodine under irradiation by visible light.¹⁶⁶



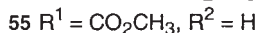
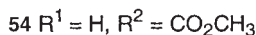
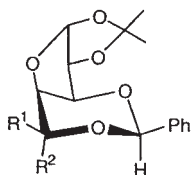
(iv) *Chain Extension of Dialdoses.*—Uronic acid derivatives can be obtained by chain extension reactions on dialdoses. Aldol condensation of “acetyl iron” $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{PPh}_3)(\text{COCH}_3)]$ with aldehydo sugar derivatives such as **50** and decomplexation of the iron led to chain-extended deoxyuronic acids (**51** and its C-5 epimer).¹⁶⁷



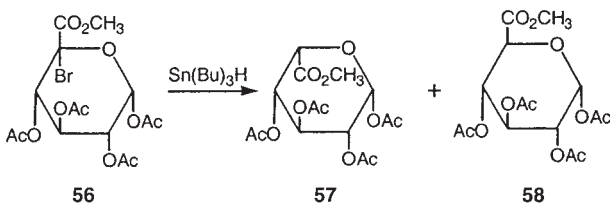
Stereocontrolled ethynylation of methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside (**52**) with a Grignard reagent formed from trimethylsilylacetylene, followed by a multistep procedure afforded the aminouronic acid **53**, the α -amino acid on which miharamycin A is based.¹⁶⁸ Uronic acid derivatives have also been produced by the Wittig reaction on the aldehydic side chain of dialdofuranose compounds.¹⁶⁹



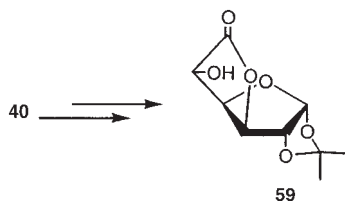
(v) **Epimerization Reactions.**—Glycuronic acids epimerize much more readily than do aldoses upon heating their aqueous solutions,¹⁷⁰ although the preparative utility of this reaction is limited by the complexity of the product mixtures. However, the reaction is useful for the synthesis of L-iduronic acid, starting from the commercially available D-glucofuranurono-6,3-lactone (**41**). Epimerization of D-glucuronic acid derivatives constrained to adopt a conformation having C-6 in axial disposition yield the more stable L-iduronic acid derivatives. Thus, methyl 3,5-O-benzylidene-1,2-O-isopropylidene- α -D-glucofuranuronate (**54**), when stored in sodium methoxide in methanol at 5 °C, yields the L-ido epimer (**55**).¹⁷¹



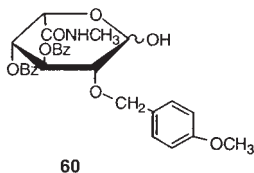
Another route involves the isomerization at C-5 of the corresponding D-glucuronic derivative via the C-bromide **56**. Compound **56** was obtained by treatment of 1,2,3,4-tetra-O-acetyl- α -D-glucopyranuronate (**58**) with *N*-bromosuccinimide. Reduction of **56** with tributyltin hydride affords the α -L-idopyranuronate derivative **57** together with the glucopyranuronate **58** (~20%), which could be separated and converted back into the bromide.¹⁷²



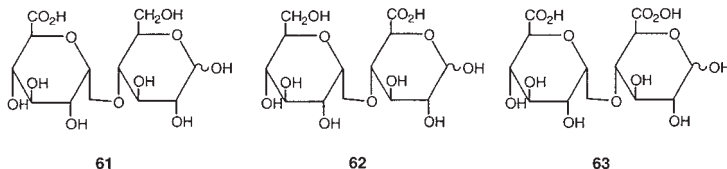
A similar rearrangement has been performed on furanasic derivatives, by a S_N2 displacement of a triflate protecting group at C-5, using sodium trifluoroacetate.¹⁷³ Thus, 1,2-O-isopropylidene- β -L-idofuranurono-6,3-lactone (**59**) has been prepared from 1,2-O-isopropylidene- α -D-glucofuranurono-6,3-lactone (**40**).



A method based on the epimerization of **40** was used for the preparation of the L-iduronic acid derivative **60**, a synthon for making glycosaminoglycan fragments.¹⁷⁴



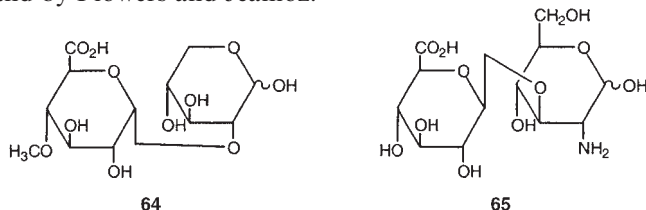
c. Oligoglycuronic Acids.—There are three main categories of disaccharides that contain glycuronic acids, namely: *aldobiouronic acids*, in which the nonreducing component is a uronic acid glycosidically linked to an aldose (or ketose); *pseudoaldobiouronic acids*, in which an aldose (or ketose) is glycosidically linked to a uronic acid; and *diglycuronic acids*, in which a glycosyluronic group is glycosidically linked to a uronic acid residue. The three types of biouronic acids are exemplified by acids **61–63**, respectively; the methyl β -glycosides of **61–63** and the free aldobiouronic acid 4-*O*-(α -D-glucopyranosyluronic acid)-D-glucose (**61**) were isolated by Abbott and Weigel after catalytic oxidation of methyl β -maltoside.¹⁷⁵



Most of the known oligoglycuronic acids are aldobiouronic acids. Because of the stability of the glycosidic linkage of aldobiouronic acids toward acid hydrolysis, they are readily isolated after vigorous hydrolysis of polysaccharides that contain uronic acid residues. They have been obtained from wood hemicelluloses, plant mucilages, gums, bacterial and animal polysaccharides, and by synthesis.

A common example that has been isolated from many plant polysaccharides is 2-*O*-(4-*O*-methyl- α -D-glucopyranosyluronic acid)-D-xylose (**64**). Hyalobiouronic acid, [2-amino-2-deoxy-3-*O*-(β -D-glucopyranosyluronic acid)-D-glucose] (**65**), whose *N*-acetyl derivative is the repeating unit of

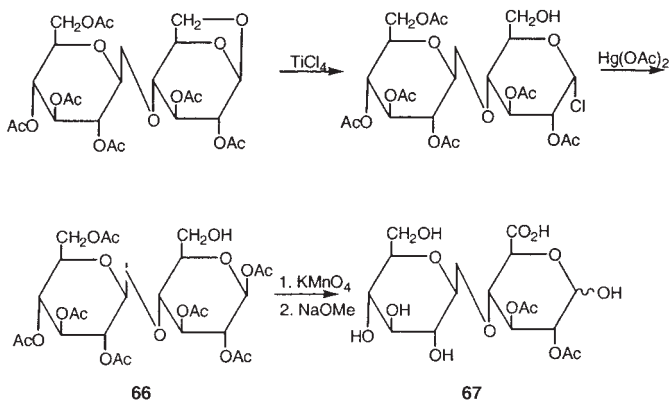
the glycosaminoglycan hyaluronic acid, has been synthesized by Takanashi *et al.*¹⁷⁶ and by Flowers and Jeanloz.¹⁷⁷



Some capsular *Streptococcus pneumoniae* polysaccharides,¹⁷⁸ for example type III, initially examined by Heidelberger and Goebel,¹⁷⁹ contain cellobiouronic acid [4-*O*-(β -D-glucopyranosyluronic acid)-D-glucose] residues. Jayme and Demmig¹⁸⁰ synthesized this acid by platinum-on-carbon-catalyzed oxidation of benzyl β -cellobioside with oxygen. It is noteworthy that only the primary alcoholic group of the D-glucose residue remote from the benzyl group is oxidized. Hydrogenolysis of the benzyl group gave the crystalline acid. Lindberg and Selleby¹⁸¹ independently prepared the acid by permanganate oxidation of the single, unprotected hydroxyl group of 2,3,2',3',4'-penta-*O*-acetyl-1,6-anhydrocellobiose. Maltobiouronic acid (**61**) has been prepared by similar methods.^{175,182}

Aldobiouronic acids have also been prepared by the Koenigs-Knorr reaction.² β -D-Glucuronic acid-containing disaccharides have been synthesized using derivatives of methyl (1-thio- β -D-glucopyranosid)uronate with different protective groups as glycosyl donors.¹⁸³

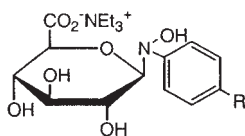
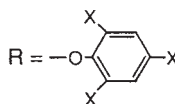
Barker *et al.*¹⁸⁴ reported the enzymic synthesis of the pseudoaldobiouronic acid, 2-*O*- α -D-glucopyranosyl-D-glucuronic acid. The synthesis of 4-*O*- β -D-glucopyranosyl-D-glucuronic acid (**67**) by permanganate oxidation of 1,2,3,2',3',4',6'-hepta-*O*-acetyl- β -cellobiose (**66**) was described,¹⁸⁵ and 4-*O*- α -D-glucopyranosyl-D-glucuronic acid was similarly prepared.¹⁸⁶



Derivatives of the digalacturonic acid units β -D-GalpA-(1 \rightarrow 2)-D-GalpA, β -D-GalpA-(1 \rightarrow 3)-D-GalpA, and β -D-GalpA-(1 \rightarrow 4)-D-GalpA have been prepared.¹⁸⁷

Di-D-galacturonic acids and higher homologues, isolated from enzymic or acid hydrolyzates of pectin, have been studied by many laboratories. Oligogalacturonic acids ("oligosaccharins") have a variety of regulatory effects in plants.¹⁸⁸ A di-D-mannuronic acid was prepared from alginic acid.¹⁸⁹

d. Modified Glycuronic Acids.—The development of suitable conditions for catalytic oxidation has permitted the preparation of the naturally occurring aminoglycuronic acids in good yield. Weidmann and Zimmerman¹⁹⁰ prepared 2-amino-2-deoxy-D-glucuronic acid by oxidation of benzyl 2-(benzyloxycarbonyl)amino-2-deoxy- α -D-glucopyranoside with oxygen-platinum dioxide; the crystalline amino acid was released by simultaneous hydrogenolysis of the benzyl and the *N*-(benzyloxycarbonyl) groups in the oxidation product. 6-Amino-6-deoxy-D- and L-glycero-D-glucio-hepturonic acids have been made following condensation between 3-*O*-benzyl-1,2-*O*-isopropylidene-D-xylo-pentodialdose and ethyl nitroacetate.¹⁹¹ *N*-Glucosyluronic derivatives of *N*-hydroxy-*N*-arylamines (**68**), required for carcinogenicity studies, were prepared from either D-glucuronic acid triethylammonium salt or D-glucurono-6,3-lactone by treatment with the corresponding arylhydroxylamines, using pyridinium perchlorate in pyridine as catalyst.¹⁹²

**68**

X = H or Cl

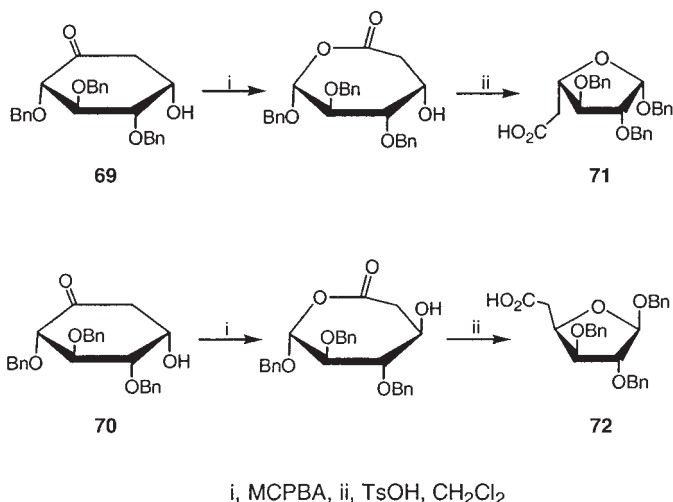
Derivatives of 2-deoxyglycuronic acids have been obtained by catalytic oxidation¹⁹³ of suitably protected alcohols, and by hydroformylation¹⁹⁴ of terminal epoxide groups in aldonic acids. 6-Deoxyhepturonic acids or derivatives thereof have been obtained by cyanide displacement of a 6-sulfonyloxy group from derivatives of hexoses and hydrolysis of the resulting nitriles.¹⁹⁵

5-Deoxy-D-xylo-hexuronic acid was obtained in good yield via the reaction of 1,2-*O*-cyclohexyliden-5-*O*-(methylsulfonyl)- α -D-glucofuranurono-1,4-lactone with hydrazine.¹⁹⁶

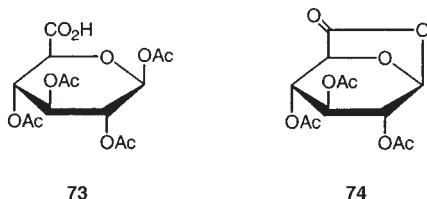
Bayer-Villiger oxidation of the Ferrier carbocyclization products **69** and **70**, derived from D-glucose, gave the isomeric 5-deoxyhexofuranosiduronic

acids **71** and **72** respectively, after acid-catalyzed rearrangement of the ring-expanded initial products.¹⁹⁷

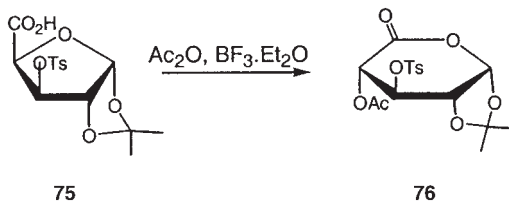
An open-chain *aldehydo*-L-guluronic acid derivative has been obtained from L-quebrachitol.¹⁹⁸



e. Properties and Reactions of Glycuronic Acids.—The uronic acids and their derivatives can exist as α and β anomers and in pyranose (**34–38**) and furanose forms; where stereochemical conditions are favorable, there is a tendency for lactone formation. Thus, whereas the crystalline glycofuranose-6,3-lactones of D-glucuronic and D-mannuronic acids are readily formed, D-galactofuranuronic acid, both anomers of which are crystalline, is unable to lactonize, because O-3 and the exocyclic C-5–C-6 chain are in a *trans* relationship with respect to the furanose ring. However, such derivatives as 2,4,5-tri-O-acetyl-D-galactofuranurono-6,3-lactone dialkyl dithioacetals and the corresponding demercaptalated aldehydo derivatives are known.¹⁹⁹ Carboxyl groups can lactonize with C-1. For example, 1,2,3,4-tetra-O-acetyl- β -D-glucopyranuronic acid (**73**) led to the corresponding 6,1-lactone (**74**) by treatment with SnCl₄ in boiling benzene.²⁰⁰



When 1,2-*O*-isopropylidene-3-*O*-tosyl- α -D-xylofuranuronic acid (**75**) was treated with acetic anhydride and a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in ethyl acetate, it was converted into the 5,1-lactone **76**.²⁰¹



Conformational investigations based on force-field studies²⁰² and NMR investigations²⁰³ have been carried out on the α -idopyranuronic acid ring in connection with the structures of certain polysaccharides. The ${}^4\text{C}_1$, ${}^1\text{C}_4$, and ${}^2\text{S}_0$ conformations were found to be significant, and sulfation exerts an appreciable influence on the conformation adopted.

The characterization and quantitative determination of uronic acid components in polysaccharides faces the problem of complete release of the uronic acids without accompanying decomposition. This is a difficult task because of the acid resistance of the glycosiduronic bond. From a comparison of several methods, it was shown that methanolysis combined with trifluoroacetic acid hydrolysis is the best for the liberation of uronic acids.²⁰⁴ The identification can be performed by gas chromatography of the trimethylsilyl derivatives.²⁰⁵

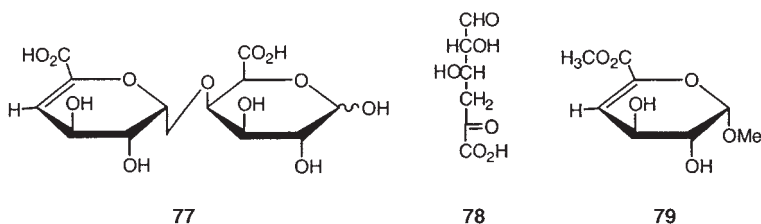
Uronic acids, together with neutral sugars of plant cell-wall materials, have been determined by high-performance liquid chromatography (HPLC) of their methyl glycosides after combined enzymic hydrolysis and methanolysis.²⁰⁶ The uronic acids can also be analyzed in a mixture of sugars, without previous derivatization, by using high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD).²⁰⁴ Identification may be improved by using HPAEC coupled with electrospray ionization tandem mass spectrometry.²⁰⁷ Oligogalacturonic acids up to 50 residues can be analyzed by HPAEC-PAD.²⁰⁸

For quantitative analysis of uronic acid residues in polysaccharides or glycoconjugates, they may be reduced to the corresponding neutral sugar residues before hydrolysis, which then proceeds without difficulty. The reduction requires two steps: activation of the carboxylic group and reduction using an alkaline hydride. Most techniques differ in the first step. The carboxyl groups may be esterified by diazomethane^{209,210} or activation can be performed by reaction with a carbodiimide.²¹¹ Reduction of the esterified units can be performed by using imidazole buffer with potassium borohydride.²¹² The methyl ester groups can be reduced by lithium

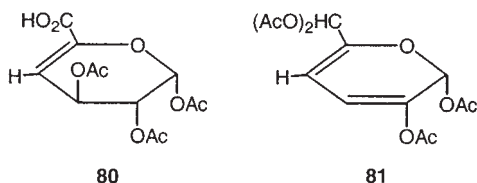
aluminum deuteride, and the methyl esters derived from uronic acid residues can then be distinguished from those derived from sugar residue by their mass spectra.²¹³

The formation of 4,5-unsaturated uronic acid residues by enzymic or alkaline degradation of polysaccharides containing uronic acids has been the object of many investigations.²¹⁴

Hasegawa and Nagel obtained the unsaturated diglycuronic acid 4-*O*-(4-deoxy- β -L-*threo*-hex-4-enopyranosyluronic acid)-D-galacturonic acid (**77**), following hydrolysis of pectic acid by a pectolytic enzyme from *Bacillus polymyxa*.²¹⁵ Preiss and Ashwell degraded a D-galacturonan by the action of an extract of a *Pseudomonas* species and isolated D-galacturonic acid and 4-deoxy-L-*threo*-hexos-5-ulosuronic acid (**78**), products of continued enzymolysis of **77**.²¹⁶ Acid **78** had been obtained by Linker *et al.* by enzymic degradation of hyaluronic acid.²¹⁷ Pectin (the partial methyl ester of pectic acid) undergoes the well-known β -elimination reaction under alkaline conditions.²¹⁸ Methyl (methyl α -D-galactopyranosid)uronate was used by Heim and Neukom as a model compound for studying this reaction, and alkaline treatment of it afforded the expected methyl (methyl 4-deoxy- β -L-*threo*-hex-4-enopyranosid)uronate (**79**).²¹⁹ Subsequent studies revealed that even poor leaving groups (for instance, isopropylidene acetals) undergo facile β -elimination under similar conditions.²²⁰ Timpe *et al.* studied the elimination-reduction reaction converting D-hexofuranosidurono-6,3-lactones into 3-deoxy-hex-2-enono-1,4-lactones by treatment with sodium borohydride in hexamethylphosphoric triamide.²²¹

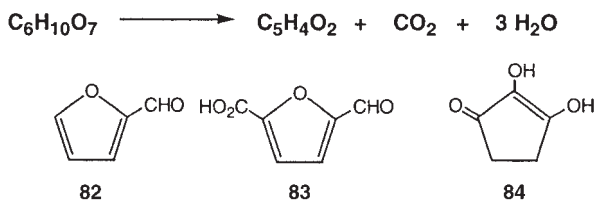


Treatment of α -D-galactopyranosyluronic acid with acetic anhydride and 4-(dimethylamino)pyridine gave alkene **80** in high yield;²²² heating in acetic anhydride together with acetic acid led to derivative **81**. The 3-keto derivative of D-glucuronic acid, D-*ribo*-3-hexulosuronic acid, has been prepared by chromic acid oxidation of methyl 5-*O*-acetyl-1,2-*O*-isopropylidene- α -D-glucofuranuronate,^{223a,223b} the 5-keto derivative of 1,2-*O*-isopropylidene- α -D-glucofuranurono-6,3-lactone (**42**) has been prepared by oxidation with manganese dioxide,²²⁴ chromium trioxide,²²⁵ or oxygen in the presence of platinum.²²⁶



One of the most important reactions of hexuronic acids and glycuronans is the decarboxylation caused by treating with strong acids (usually $\sim 12\%$ hydrochloric acid). The rapid and stoichiometric loss of 1 mol of carbon dioxide per mole has been developed as an analytical method by many workers.²²⁷ Methods based on the formation of colored phenolic compounds in strongly acidic media are widely used to assay total uronic acid.^{228,229} The method of Blumenkrantz and Asboe-Hausen²²⁸ has been adapted for microtiter plates.²³⁰

The mechanism of acid-catalyzed decarboxylation of hexuronic acids has been the subject of many investigations.^{231,232} The formation of carbon dioxide is accompanied by the formation of 2-furaldehyde, $C_5H_4O_2$ (**82**) as the main product, along with considerable amounts of "humins"; however, both 5-formyl-2-furoic acid (**83**) and reductic acid (**84**) have been isolated as end products from treatment of hexuronic acids with strong acid.



Feather and Harris, using ^{14}C -labeled uronic acids, proved that the 2-furaldehyde (**82**) contained over 99% of the label in the aldehyde group, whereas compound **84** appeared to be formed via two different mechanisms. D-Galacturonic acid, D-glucurono-6,3-lactone, alginic acid, D-xylo-5-hexulosonic acid, and D-arabino-hexulosonic acid all produce **84**, but only D-galacturonic acid and D-xylo-5-hexulosonic acid produce compound **83**. Pentoses gave none (or less than 1%) of **84**, and no pentoses could be detected during the decomposition of compounds that were sources of **84**.²³³

Zweifel and Deuel demonstrated that glycuronic acids are decarboxylated under relatively mild conditions in the presence of heavy metals; thus, L-arabinose is produced from D-galacturonic acid.²³⁴ This decarboxylation, which appears to follow a different mechanism from the one already

mentioned, was practically complete in pyridine at 100 °C with nickel acetate as the catalyst, but was slower in an aqueous medium.

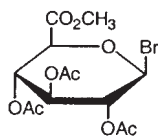
α -D-Glucofuranurono-6,3-lactone reacts with aqueous calcium hydroxide at room temperature to afford, in yields up to 70%, D-lyxo-5-hexulosonic acid, which precipitated from the reaction mixture after 11 days.²³⁵ On heating D-glucuronic acid in aqueous solution at pH 7, the following products were identified: D-lyxo-5-hexulosonic (main product), L-ribo-5-hexulosonic acid, D-mannuronic, D-altruronic, D-alluronic,²³⁶ and later, L-ribo-4-hexulosonic acid.²³⁷ Conditions to include pH, temperature, solvent, cations present, and the nature of the glycuronic acid strongly influence the transformation and degradation of uronic acids and the proportions of products formed. Degradation products from oxidative and nonoxidative treatment of D-galacturonic acid with alkali have been analyzed by GLC-MS; 13 hydroxy monocarboxylic acids and 26 dicarboxylic acids were identified, in addition to several isomerization products.²³⁸

The reducing group in uronic acids can be oxidized by nitric acid or bromine to yield aldarcic acids. Uronic acids, as salts, can be quantitatively reduced to aldonic acids by borohydride.²³⁹ Lactones are readily reduced, as in the controlled conversion of D-glucurono-6,3-lactone into D-glucosylhexodialdose. The carboxyl group of glucuronic acids may be reduced to a primary alcoholic group.

The presence of both aldehyde and carboxylic acid groups in uronic acids allows the formation of different types of derivatives. Phenylhydrazine may react with uronic acid derivatives to form hydrazides, hydrazones, or osazones. Amides and benzimidazoles are useful as characterizing derivatives. Esterification and glycosylation are competing reactions when uronic acids are treated with an alcohol under acidic conditions. D-Galacturonic acid reacts with methanolic hydrogen chloride to undergo esterification 25–55 times as fast as glycoside formation.²⁴⁰ However, when the reaction is performed in heterogeneous media by using tetrahydrofuran as the solvent and ferric chloride as promoter, methyl D-galactosiduronic acids are obtained in ~70% yield as a mixture of furanosides and pyranosides. In the presence of calcium chloride, the alkyl- β -D-galactofuranosiduronic acids were obtained in good yield. In the case of D-glucuronic acid, the glycosides are obtained as the glucofuranosidurono-6,3-lactones, which can be hydrolyzed under mildly alkaline conditions to afford the (alkylglucofuranosid)uronates.²⁴¹

Base-catalyzed esterification of D-glucurono-6,3-lactone proceeds smoothly at room temperature.²⁴² The acetylated glycuronic acids, and the per-O-acetylglucosyluronic halides of their methyl esters, are important precursors for the synthesis of glycosiduronic acids. D-Glucofuranurono-6,3-lactone

reacts with acetic anhydride in pyridine to form mainly 1,2,5-tri-*O*-acetyl- α -D-glucofuranurono-6,3-lactone, whereas zinc chloride²⁴³ or boron trifluoride²⁴⁴ catalyzes formation of the β anomer as the main product. Acetylation of methyl D-glucopyranuronate with acetic anhydride in the presence of various catalysts gives mixtures of the α and β anomers of methyl 1,2,3,4-tetra-*O*-acetyl-D-glucopyranuronate,²⁴² which can be converted into methyl 2,3,4-tri-*O*-acetyl-1-deoxy-1-halo-D-glucopyranuronates. A number of β -D-glucopyranosiduronic acids have been prepared from methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy- β -D-glucopyranuronate (**85**), a compound initially prepared by Goebel and Babers by the action of hydrogen bromide in acetic acid on methyl tetra-*O*-acetyl- α - or β -D-glucopyranuronates.²⁴⁵



85

Both anomers of D-glucopyranosyluronic acid phosphate have been synthesized; this has made possible the synthesis of uridine 5'-(α -D-glucopyranosyluronic acid diphosphate).¹⁰³

Glycosides of unprotected D-glycuronic acids have been formed directly in the appropriate alcohol with boron trifluoride etherate as catalyst, affording D-glycosiduronates.²⁴⁶ D-Glucosyluronic acid trichloroacetimidate has also been used for glycosylation of uronic acids.²⁴⁷

The relative reactivity of L-iduronic acid derivatives as glycosyl donors is noteworthy. The trichloroacetimidate and *n*-pentyl glycosides are the most effective, and are more reactive than the corresponding thioglycosides or glycosyl fluorides.²⁴⁸ The trichloroacetimidate method has been used in high-yielding synthesis of disaccharide blocks, useful for the preparation of complex oligosaccharides related to heparin, heparan sulfate, and dermatan sulfate.

3. Aldaric Acids

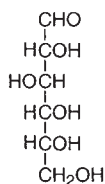
Aldaric acids (previously called saccharic acids) are polyhydroxy dicarboxylic acids, $\text{HO}_2\text{C}(\text{CHOH})_n\text{CO}_2\text{H}$, that are formally produced by oxidation of aldoses at both termini; they are primarily obtained from sugars, aldonic acids, and oligo- or poly-saccharides by reaction with strong oxidizing agents. They are named systematically by replacing "ose" in the name of the corresponding aldose by "aric acid," although there are also

many established trivial names. End-to-end symmetry allows internal compensation, so that various *meso* (optically inactive) forms exist, and different aldoses may afford identical aldaric acids. For instance, D-glucose and L-gulose give the same acid: D-glucaric acid = L-gularic acid (**86**). The former name, appearing first in the alphabet, is favored; D-glucaric acid is also occasionally described by the obsolete trivial name, saccharic acid. Characteristic, difficultly soluble acidic salts and many aldarolactones are known.

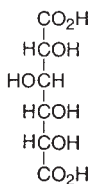
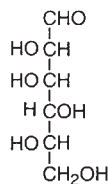
There are four pentaric acids and ten hexaric acids:

Pentaric acids (sometimes known as hydroxyglutaric): ribaric (*meso*), xylaric (*meso*), and D- and L-arabinaric (D- and L-lyxaric).

Hexaric acids: allaric (*meso*), formerly *allo-mucic*; galactaric (*meso*), formerly *mucic*; D- and L-glucaric (L- and D-gularic), formerly D- and L-*gluco*-saccharic; D- and L-mannaric, formerly D- and L-manno-saccharic; D- and L-idaric, formerly D- and L-ido-saccharic; and D- and L-altraric (D- and L-talaric), formerly D- and L-*talo*-mucic acid.



D-glucose

**86**

L-gulose

a. Occurrence and Preparation.—Several of the hexaric acids are of special interest. Galactaric acid was first isolated by Scheele in 1780, produced by the oxidation of lactose. Its low solubility in water is characteristic, and it has been utilized in the quantitative determination of D- and L-galactose in oligo- and poly-saccharides following oxidation with nitric acid and isolation of galactaric acid from the products. Interestingly, the peracetate of galactaric acid is more soluble in water than is galactaric acid itself. The acid lactonizes with difficulty, whereas 2-deoxy-D-*lyxo*-hexaric acid, prepared from 2-deoxy-D-*lyxo*-hexose by oxidation with nitrogen dioxide, readily forms a monolactone.²⁴⁹

D-Glucaric acid was reported to occur as the magnesium salt in the sap of *Ficus elastica*,²⁵⁰ and 3-deoxy-manno-heptaric acid (cerheptaric acid) has been found to be widely distributed in the *Cereus* and *Trichocereus* genera of the Cactaceae family.²⁵¹

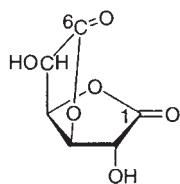
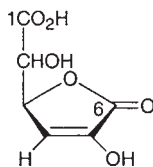
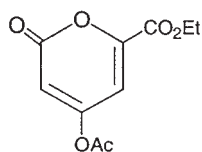
D-Glucaric acid is readily prepared by oxidation of D-glucose or starch with nitric acid, as described by Bose *et al.*,²⁵² who also developed a

procedure for the isolation of the 1,4- and 6,3-lactones. The acid is generally characterized as the potassium hydrogen salt. The 1,4-lactone, which has been shown by Levvy²⁵³ to have specific anti(β -D-glucosiduronase) activity, has applications as a biochemical reagent.²⁵⁴

Aldaric acids may be prepared from aldoses or aldonic acids by oxidation in aqueous solution with oxygen over platinum-charcoal²⁵⁵ or platinum-on-alumina.²⁵⁶ The effect of such promoters as bismuth or gold has also been studied.²⁵⁷ Hydrogen peroxide in the presence of iron salts has been used for the oxidation of uronic acids to aldaric acids.²⁵⁸

The electrocatalytic oxidation of D-gluconic acid at an ubiquinone-mixed carbon paste electrode with an immobilized layer of D-gluconate dehydrogenase has been described.²⁵⁹

b. Properties and Reactions.—D-Glucaric and D-mannaric acids yield dilactones, which reduce Fehling solution, and the same behavior is shown by the ester lactones of D-glucaric acid. Smith *et al.*²⁶⁰ attributed the reducing character to the opening of a lactone ring by the alkaline reagent, with subsequent formation of an enol, as exemplified by the conversion of the 1,4:3,6-dilactone (**87**) of D-glucaric acid (**86**) into **88**. In alkaline solution, ozone attacks the double bond, affording oxalic acid and L-threuronic acid. Reaction with diazomethane affords an esterified enol ether.

**87****88****89**

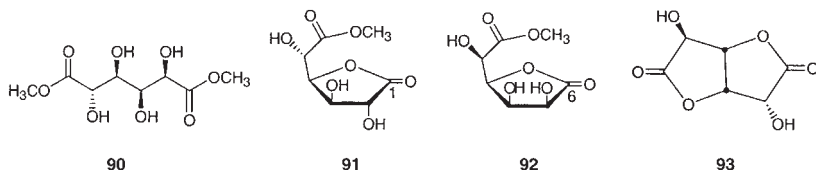
Morgan and Wolfrom isolated an α -pyrone, probably 4-acetoxy-6-(ethoxycarbonyl)-2H-2-pyrone (**89**), from the reaction of monoethyl DL-galactarate or its monolactone with acetic anhydride and sodium acetate at 100 °C; the authors postulated the intermediate formation of an enolic lactone in this transformation.²⁶¹

Aldaric acids or their derivatives undergo ready epimerization in pyridine. Alkaline treatment of 4-O-methyl-D-glucuronic acid in the presence of air affords 4-O-methyl-D-glucaric and -D-mannaric acids as well as lower O-methylaldaric acids.²⁶² The two diastereoisomeric 3-deoxy-2-C-(hydroxymethyl)pentaric acids obtained from

4-*O*-methyl-D-glucuronic acid have also been obtained by treatment of alginates with alkali.²⁶³

Conformations of the D-glucarolactones and D-glucaric acid in solution have been investigated by ¹H and ¹³C NMR spectroscopy.²⁶⁴

Treatment of D-glucaric acid (**86**) with acidic methanol gives a mixture of dimethyl D-glucarate (**90**), methyl D-glucarate-1,4-lactone (**91**), methyl D-glucarate-6,3-lactone (**92**), and thorough drying under vacuum, led to dilactone **93**. The equilibria between the various species were studied in both acidic and basic methanol.²⁶⁵



Several acyclic derivatives have been synthesized, including acetals of dimethyl D-glucarate.²⁶⁶ Others include diamides of aldaric acids²⁶⁷ and the bis(2-chloroethyl)amides.^{267a} Amides of D-glucaric acid have been polymerized to give hydroxylated nylons without the need to protect hydroxyl groups.^{267b}

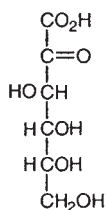
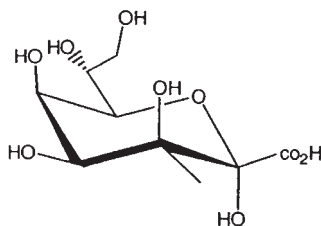
Escherichia coli metabolizes D-glucaric acid and galactaric acid to give respectively 3-deoxy-D-erythro-2-hexulosaric and 3-deoxy-L-threo-2-hexulosaric acids.²⁶⁸

4. Modified Aldonic Acids

This section deals with acids, that are formally modified aldonic acids, such as keto, deoxy, and branched-chain acids (including the so-called saccharinic acids). The aminoaldonic acids, which are oxidation products of amino sugars, and, in particular, the important nonulosaminic acids (neuraminic acids) and muramic acid, are not discussed here. The formation of saccharinic acids by the treatment of sugars with alkali, and the mechanisms involved, are likewise outside the scope of this chapter.

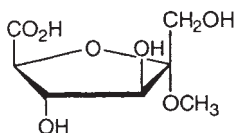
a. Glycosonic Acids (“Ketoaldonic Acids”).—(i) Occurrence.—The most important glycosonic acids are the 2-keto acids, and the 5-keto acids of the hexose series (or 4-keto acids in the pentose series). The latter have also been termed *keturonic acids* (glycuronic acids related to ketoses). D-arabino-2-Hexulosonic acid (**94**) was characterized as a minor

component in a polysaccharide obtained from the fungus *Cyttaria hariatii*.²⁶⁹ A 2-octulosonic acid, namely D-glycero-D-talo-oct-2-ulopyranosylonic acid (Ko, **95**) is a constituent of the main chain in the LPS core from bacteria of the *Acinetobacter* genus. Thus, Ko replaces the 3-deoxy-D-manno-octulosonic acid (Kdo) present in the core region of most LPS of Gram-negative bacteria.²⁷⁰ Neoglycoproteins containing Ko have been prepared.²⁷¹

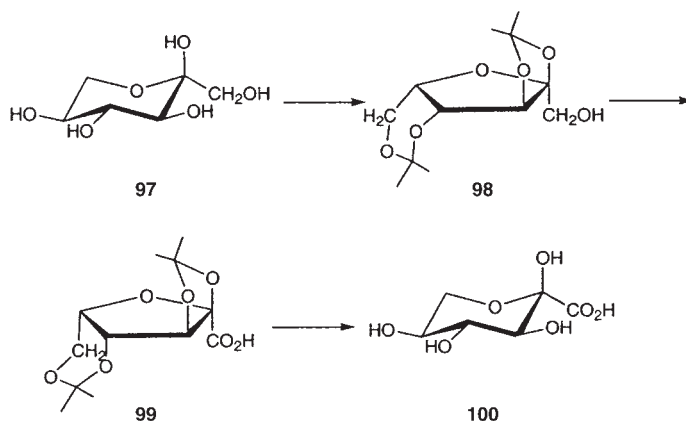
**94****95**

(ii) **Synthesis and Reactions.**—The glyculosonic acids are usually prepared by chemical or enzymic oxidation of hexoses or aldonic acids, or by isomerization of glycuronic acids. 2-Aldulosonic acids have been investigated primarily as intermediates in the synthesis of L-ascorbic acid, to which they are readily enolized. 2-Glyculosonic acids can be produced in high yield by oxidation of aldoses or aldonic acids in aqueous solution with oxygen, in the presence of a Pt–C catalyst modified with a lead(II) salt.²⁷² D-arabino-2-Hexulosonic acid (“2-keto-D-gluconic acid,” **94**) has also been produced by electrochemical oxidation of D-glucose.²⁷³

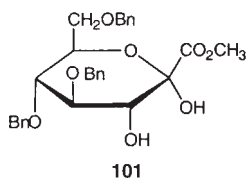
Catalytic oxidation of methyl α -D-fructofuranoside over Pt–C led to the uronic acid **96**, which is the methyl- α glycoside of D-lyxo-5-hexulosonic acid.¹⁵⁵

**96**

L-xylo-2-Hexulosonic acid (“2-keto-L-gulonic acid,” **100**), an important intermediate in the synthesis of L-ascorbic acid (see Section II.5), is obtained by oxidation of 2,3:4,6-di-O-isopropylidene-L-sorbose (**98**) with potassium permanganate or other oxidants.²⁷⁴

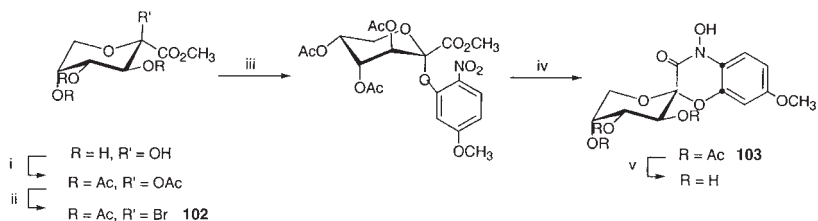


Derivative **101** of D-*gluco*-heptulosonic acid is accessible by hydroxylation of a 2,3-ene precursor.²⁷⁵



The D-*arabino*-hex-2-ulopyranosonates have been used as building blocks for the synthesis of spiroheterocyclic carbohydrates.^{276,277} The glycosyl donor, methyl (3,4,5-tri-*O*-acetyl- β -D-*arabino*-hex-2-ulopyranosyl)onate bromide (**102**), obtained from the methyl ester of D-*arabino*-2-hexulosonic acid may be converted into its nitrophenyl α -glycoside, which in turn is reductively cyclized to the spirane **103** (Scheme 8).

Methyl 5-hexulosonates are the products of oxidation with chromium trioxide of acylated methyl β -D-hexopyranosides, which adopt the 4C_1

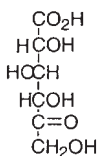


i, Ac₂O, H₂SO₄, 60°C; ii, HBr, HOAc; iii, 5-methoxy-2-nitrophenol, K₂CO₃, acetone, reflux; iv, H₂, Pt/C, MeOH; v, NaOMe, MeOH.

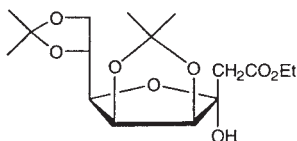
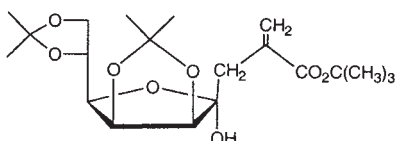
SCHEME 8

conformation.²⁷⁸ This was described as a method to distinguish them from the α -D-glycopyranosides, which are not so oxidized. D-*xylo*-5-Hexulosonic acid (**104**) is, however, best prepared by the action of *Acetobacter suboxydans* on D-glucose.²⁷⁹ The same organism also dehydrogenates D-arabinonic acid to the 4-aldulosonic acid. D-*lyxo*-5-Hexulosonic acid was prepared in 70% yield by tautomerization of D-glucurono-6,3-lactone in aqueous calcium hydroxide solution.²³⁵ Reduction of 5-aldulosonic acids has been used for the preparation of aldonic acids of the L series.

The rather unstable D-*threo*-2,5-hexodiulosonic acid was obtained by the oxidation of D-glucose with *Acetobacter melanogenum*.²⁸⁰ 2,3-Diulosonic acids are formed by oxidation of L-ascorbic acids (see Section II.5), and their formation by oxidation with hydrogen peroxide is discussed in the following chapter.

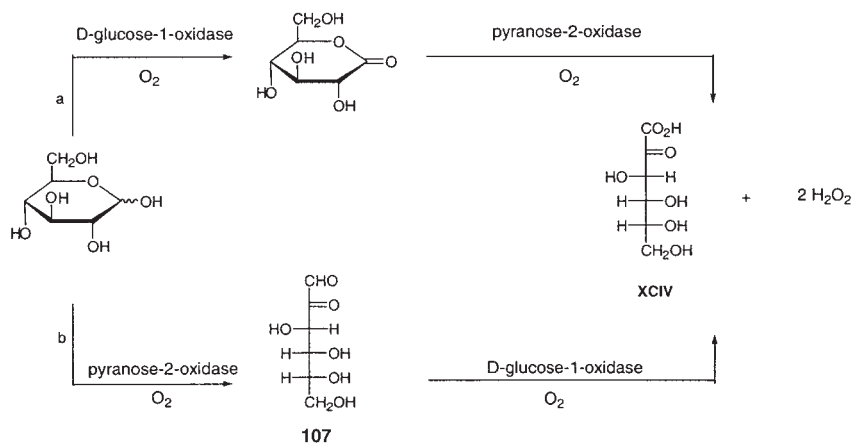
**104**

3-Glyculosonates of type **105** and 4-glyculosonates such as **106** were prepared from protected aldono-lactones by Reformatsky-like reactions.²⁸¹ Similar products, with either furanose or pyranose rings, can also be made from aldono-lactones by using such reagents as ethyl 2-trimethylsilylacetate in the presence of tetrabutylammonium fluoride.²⁸²

**105****106**

A number of papers describe the preparation of glyculosonic acids by bacteria. The genus *Pseudomonas* is reported to be particularly efficient for the preparation of D-*arabino*-2-hexulosonic acid (**94**), a compound used on the industrial scale for production of isoascorbic acid. Lockwood described the preparation of **94** in good yield by such a strain.²⁷⁹ 2-Glyculosonic acids can be degraded to lower aldonic acids by the Ruff procedure.

The enzymatic reaction for forming D-*arabino*-2-hexulosonic acid (**94**) from D-glucose may follow one of the two pathways (Scheme 9, Path a).



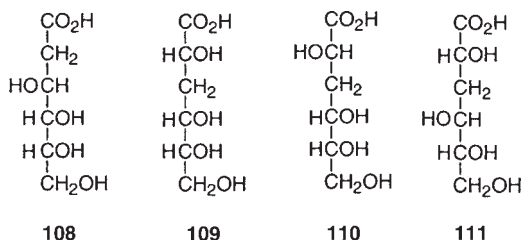
SCHEME 9

One of them involves the enzymes D-glucose-1-oxidase (EC 1.1.3.4) and pyranose-2-oxidase (EC 1.1.3.10). An alternative enzymatic pathway (Scheme 9, Path b) requires the same two enzymes, but proceeds through the intermediate *D-arabino*-hexos-2-ulose, “*D-glucosone*,” (**107**); the enzyme catalase can be used to decompose the H_2O_2 .²⁸³

b. Deoxyaldonic Acids.—Many deoxyaldonic acids and derivatives have been prepared;²⁸⁴ oxidation of deoxyaldoses is the usual source, and bromine water, permanganate, and barium hypoiodite are commonly used as oxidants. 2-Deoxy-*D-arabino*-hexonic acid (**108**) or its lactone can be obtained crystalline in three steps from tri-*O*-acetyl-*D*-glucal;²⁸⁵ the 6-phosphate of **108** has also been prepared.²⁸⁶ Acetylated diazomethyl ketoses undergo the so-called Wolff rearrangement to give 2-deoxyaldonic acids⁹⁵ (see Section II.1.b.iii). A synthesis of 2-deoxyaldonolactones by a one-step α -deoxygenation, mediated by samarium diiodide, was described.²⁸⁷ 2-Deoxyaldonolactones behave as typical aldonolactones, in that the rates of hydrolysis of the 1,5-lactones far exceed those of the 1,4-lactones. It is significant, however, that 2-deoxyaldono-1,4-lactones are considerably more stable than the corresponding aldono-1,4-lactones.⁵⁹

The 3-deoxyaldonic acids (metasaccharinic acids) arise by alkaline treatment of monosaccharides, especially those substituted at C-3.²⁸⁸ They have also been obtained from (1 \rightarrow 3)-linked oligo- and polysaccharides. The most common ones are 3-deoxy-*D-ribo*-hexonic acid (α -*D*-glucometasaccharinic acid, **109**) and 3-deoxy-*D-arabino*-hexonic acid (β -*D*-glucometasaccharinic acid, **110**), which can most conveniently be

prepared by treatment of 3-*O*-methyl-D-glucose or laminaran with lime water.²⁸⁹ Compounds **109** and **110** are obtained together, but they can be isolated in pure form by fractional recrystallization of their calcium salts. The 1,4-lactones of **109** and **110** are also crystalline. Reversible epimerization of the lactones results from alkaline treatment or heating. The conversion of 2-deoxy-D-*erythro*-pentose into **109** and **110** via the cyanohydrin synthesis and the reduction of the intermediate 3-deoxyaldono-1,4-lactones to the corresponding 3-deoxyaldoses was described by Wood and Fletcher.²⁹⁰ Conversely, the biologically significant sugar 2-deoxy-D-*erythro*-pentose is available by Ruff degradation of **109** or **110**.²⁹¹



The metasaccharinic acids produced by the action of lime water on D-glucose may be used for this synthesis without isolation. Both the 5-phosphates and the 6-phosphates of mixtures of **109** and **110** have been prepared.²⁹²

3-Deoxy-D-*xylo*-hexonic acid (α -D-galactometasaccharinic acid, **111**) can be prepared from D-galactose;²⁸⁹ the β -(D-*lyxo*) isomer can be isolated in smaller amounts from the mother liquors.

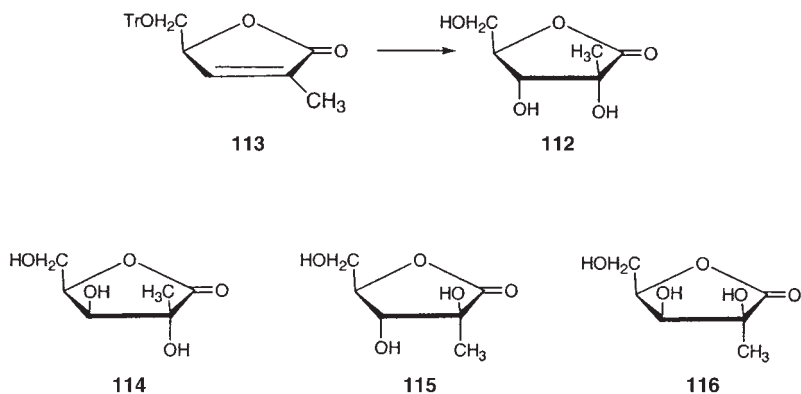
Dideoxyaldonic acids have been prepared by hydrogenation of derivatives of the intermediate (*E*)-2,3-dideoxyald-2-enonic acids in the aldonic acid synthesis of Kochetkov and Dmitriev.⁴¹

Deoxy- and dideoxy-aldonolactones have also been prepared via the bromo derivatives, which on hydrogenolysis yield the corresponding deoxyaldonolactones.²⁹³ 3-Deoxyaldonolactones have been obtained via β -elimination reactions on aldonolactones and catalytic hydrogenation of the intermediate 2-enonolactone derivatives.³⁷ The synthetic potential of this reaction was used for the synthesis of 3-deoxyaldonolactones by combining the base-catalyzed elimination of peracylated lactones with the *in situ* reduction.²⁹⁴

c. Branched-Chain Aldonic Acids.—This group includes saccharinic acids,²⁸⁸ which are products of the alkaline degradation of sugars, together

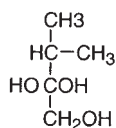
with synthetic acids prepared by condensation reactions or by oxidation of branched-chain sugars.

2-*C*-Methyl-D-ribonic acid (α -D-glucosaccharinic acid) is readily prepared by the action of lime water on D-fructose or "inverted" sucrose. It was isolated as the crystalline calcium salt, or as the 1,4-lactone (**112**).²⁸⁹ The configuration of the acid was correlated with that of the branched-chain sugar 2-*C*-(hydroxymethyl)-D-ribose (hamamelose).²⁹⁵ The yield is low (10%) and the reaction time is very long. Compound **112** is useful in the synthesis of products of pharmacological interest.²⁹⁶ 2-*C*-Methyl-D-ribono-1,4-lactone (**112**) has been made by stereoselective hydroxylation (KMnO₄, crown ether) of the unsaturated compound **113** available from 2,3-*O*-isopropylidene-D-glyceraldehyde by a Wittig sequence.

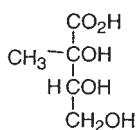


A similar approach, but using hydroxylation with osmium tetroxide, was applied for the preparation of 2-*C*-methyl-D-xylo-1,4-lactone (**114**), 2-*C*-methyl-D-arabinono-1,4-lactone (**115**), 2-*C*-methyl-DL-lyxono-1,4-lactone (**116**, for the D isomer), and 2-*C*-methyl-DL-ribono-1,4-lactone (**112** for the D isomer).²⁹⁷

Ishizu *et al.*²⁹⁸ found that D-xylose and D-fructose react with aqueous calcium hydroxide to produce 13 lactonizable saccharinic and other acids. These were identified after separation by cellulose column and gas-liquid chromatography, and the C₅-saccharinic acids, 2-*C*-methyl-D-threonic acid (**117**) and 2-*C*-methyl-D-erythronic acid (**118**), were among those isolated. These authors²⁹⁹ later reported that L-sorbose reacts similarly, to generate 14 lactones, including the 2-*C*-methyl-L-xylo-1,4-lactone and 2-*C*-methyl-L-lyxono-1,4-lactone, which were also prepared from 1-deoxy-L-threo-pentulose via the cyanohydrin reaction.



117

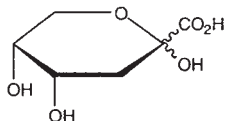


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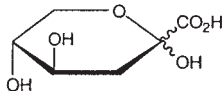
3-Deoxy-2-*C*-(hydroxymethyl)-*D*-*erythro*-pentonic acid (α -*D*-*gluco*-isosaccharinic acid) is more conveniently prepared by treatment of 4-*O*-substituted *D*-glucose derivatives, such as lactose, maltose, and cellobiose with lime water,²⁸⁹ although it is also found among the numerous products of alkaline decomposition of *D*-glucose, *D*-mannose, and *D*-fructose. The acid can be isolated as its crystalline calcium salt or the 1,4-lactone. The configuration of C-2 was finally settled by X-ray crystallography.³⁰⁰ The two epimers were found to be formed in approximately equal amounts on treatment of various 4-*O*-methyl-*D*-glucose derivatives with aqueous calcium hydroxide.

The five-carbon isosaccharinic acid, 3-deoxy-2-*C*-(hydroxymethyl)-*DL*-*glycero*-tetronic acid, was obtained from alkali-degraded oligo- and polysaccharides containing β -(1 \rightarrow 4)-linked *D*-xylose residues.³⁰¹

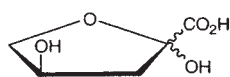
d. Deoxyketoaldonic Acids.—(i) *Occurrence.*—The 3-deoxy-2-glycoso-*nic* acids are of biochemical importance. The 2-keto-3-deoxy-*D*-hexonic acids having the *D*-*erythro* (119) or *D*-*threo* (120) configurations, and 3-deoxy-*L*-*glycero*-pent-2-ulosonic acid (121) are well-known metabolites in the oxidative degradation pathway of aldoses leading to pyruvate and hydroxyaldehydes.^{302,303}



119



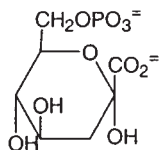
120



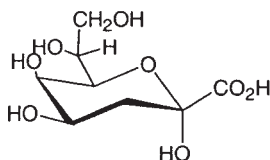
121

There are also reports of their occurrence in polysaccharides. 3-Deoxy-*D*-*threo*-hex-2-ulosonic acid (120) is a component in the extracellular polysaccharide of *Azotobacter vinelandii*³⁰⁴ and 3-deoxy-*L*-*glycero*-pent-2-ulosonic acid (121) has been found as a component of the capsular polysaccharide of *Klebsiella* type 38.³⁰⁵

3-Deoxy-*D*-*arabino*-hept-2-ulosonic acid-7-phosphate ("DAHP," 122) is the precursor for the synthesis of aromatic amino acids in all micro-organisms and plants (shikimic pathway).^{306,307}



122



123

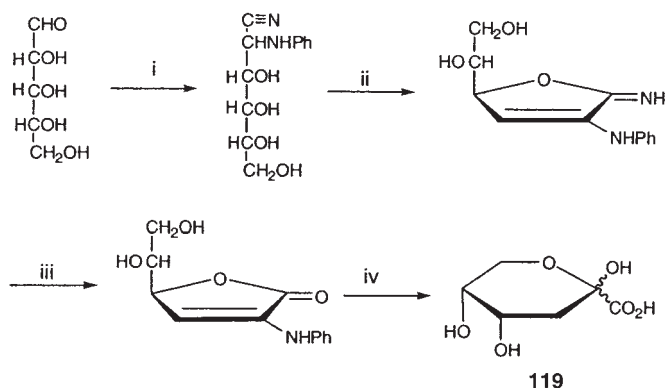
As a component of a natural glycoconjugate, the best-known example is 3-deoxy-D-*manno*-oct-2-ulonic acid (**123**), commonly known as Kdo. Compound **123** is part of the core linking the polysaccharide to lipid A in the LPS that is characteristic of Gram-negative bacteria.³⁰⁸ Kdo is usually found in the α -pyranosic configuration, but it may exist as furanoside as in the LPS of *Bordetella pertussis*.³⁰⁹

(ii) *Synthesis*.—Four main methods have been used for the chemical synthesis of deoxyketoaldonic acids, as detailed below.

Selective oxidation at C-2 of 3-deoxyaldonic acids by the action of sodium perchlorate in the presence of vanadium pentaoxide has been used for the preparation of deoxyketoaldonic acids, although low yields of pure compounds are obtained. The necessary 3-deoxyaldonic acids may be prepared by a cyanohydrin chain-extension reaction. Several syntheses have been reported for 3-deoxy-D-*arabino*-hept-2-ulonic acid starting from 2-deoxy-D-*arabino* hexose,^{310,311} DAHP (**122**) has also been similarly prepared.³¹²

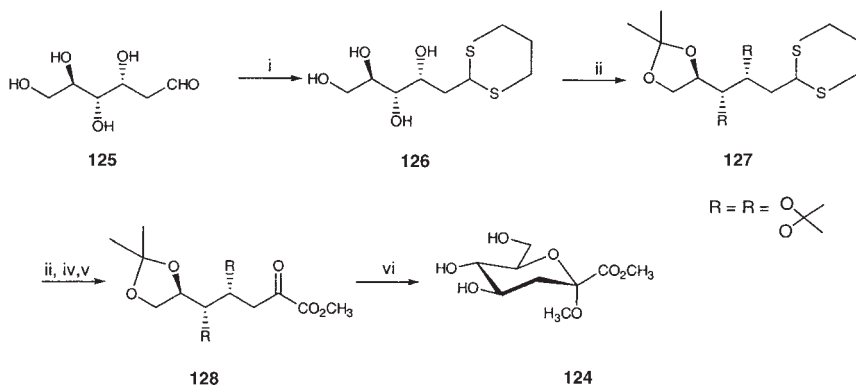
Chain-extension reactions constitute a more widely used approach. Thus, the cyanohydrin synthesis followed by base-catalyzed cyclization and β -elimination to iminolactones, which then undergo stepwise hydrolysis, affords 3-deoxy-2-glyculosonic acids.³¹³ The overall yield of this reaction is low. Paerels³¹⁴ used this method to prepare the first crystalline members of this group, namely 3-deoxy-D-*erythro*-hex-2-ulosopyranosonic acid (2-keto-3-deoxy-D-gluconic acid, KDG, **119**), and the L isomer, starting from D-ribose and L-arabinose, respectively. The synthesis of **119** is illustrated in Scheme 10.

The synthesis of methyl (methyl 3-deoxy-D-*arabino*-heptulopyranosid)-onate (**124**) is shown in Scheme 11. 2-Deoxy-D-*arabino*-hexose (**125**) is converted into the propylene dithioacetal (**126**) which reacts with acetone to give 2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-*arabino*-hexose propylene dithioacetal (**127**). Treatment of **127** with *n*-butyllithium is followed by reaction with methylchloroformiate and removal of the dithioacetal with *N*-bromo-succinimide gives **120**. Removal of the isopropylidene groups afforded **124**.³¹²



i, PhNH_2 , HCN ; ii, KOH ; iii, H^+ ; iv, H_3O^+ , 70°C .

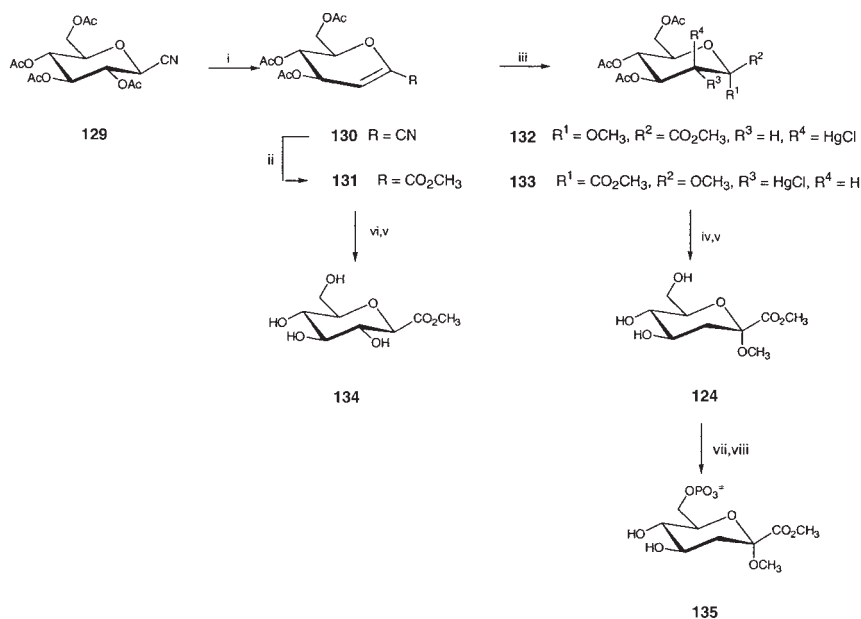
SCHEME 10



i, $\text{HCl}-\text{HS}(\text{CH}_2)_3\text{SH}-\text{EtOH}$; ii, $(\text{CH}_3)_2\text{CO}-\text{H}_2\text{SO}_4$; iii, $n\text{-BuLi}$; iv, CH_3OCOCl ; v, N -bromosuccinimide-acetone; vi, $\text{HBr}-\text{MeOH}$.

SCHEME 11

A general approach for the synthesis of these glyculosonic acids is based in the C-1 elongation of glycals. Thus, 3-deoxy-D-arabino-hept-2-ulonic acid (DAH) was synthesized starting from the glucopyranosyl cyanide derivative **129** which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the cyanoglucal **130** in 70% yield. Alkaline hydrolysis of **130** followed by acetylation and esterification of the carboxyl group



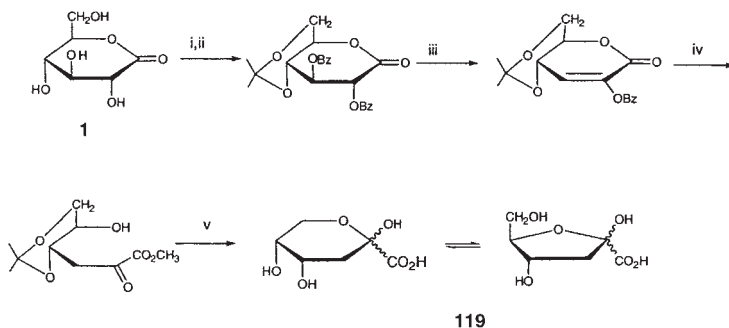
i, DBU, CH₂Cl₂; ii, 1. NaOH_{aq}-EtOH, 2. Ac₂O-Py, 3. CH₂N₂·Et₂O, iii, 1. Hg(CF₃CO₂)₂-MeOH, 2. KCl; iv, Ph₃SnH, toluene; v, (CH₃)₃SiCl, MeOH or NaHCO₃, MeOH; vi, Pd-C, H₂, EtOH; vii, (PhO)₂POCl, Py; viii, PtO₂, H₂, EtOH.

SCHEME 12

afforded the hep-2-enonate (**131**) in good yield. Methoxymercuration followed by reductive removal of the mercuri residue and deacetylation gave methyl (methyl 3-deoxy- α -D-arabino-hept-2-ulopyranosid)onate (**134**). The analogue methyl 2,6-anhydro-3-deoxy-D-gluco-heptonate (**134**) was obtained by hydrogenation of the double bond of **131**, and deacetylation. The 7-phosphate **135** was also prepared by phosphorylation of **124**³¹⁵ (Scheme 12).

Several approaches have been developed for the synthesis of 3-deoxy-D-manno-oct-2-ulosonic acid (Kdo, **123**); the most common one involves the coupling of oxaloacetic acid with D-arabinose followed by decarboxylation. This aldol reaction takes place under basic conditions, but above pH 11 side reactions occur. The procedure is simple and Kdo is isolated as the crystalline ammonium salt.³¹⁶

In a third general approach, 2-keto-3-deoxyaldonic acids are prepared from 2-enonolactones. These precursors are readily prepared in good yield by β -elimination reactions on the protected lactones.³⁷ Starting from

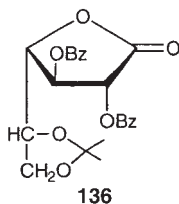


i, 2-Methoxypropene, H⁺; ii, BzCl, Py; iii, Et₃N, CH₂Cl₂, iv, NaOMe, MeOH;
 v, a) NaHCO₃, b) IR-120(H⁺).

SCHEME 13

D-glucono-1,5-lactone (**1**), 3-deoxy-D-*erythro*-hex-2-ulosonic acid (**119**) was synthesized in six steps with 45% overall yield (Scheme 13).³¹⁷

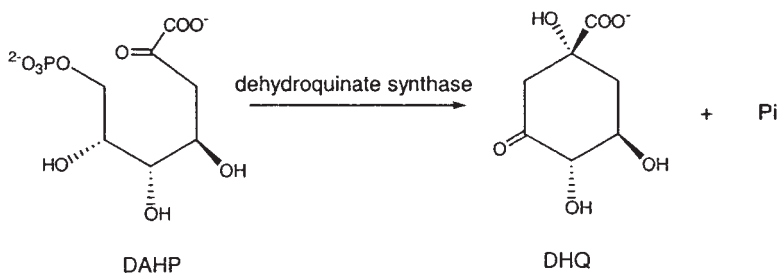
Starting from D-galactono-1,4-lactone, 2-keto-3-deoxy-D-hexonic acids with either the D-*erythro* (**119**) or D-*threo* configuration (**120**) were obtained in only three steps.³¹⁸ Epimerization at C-4 occurred during the base-catalyzed β -elimination reaction on the galactonolactone derivative **136**.



Furanose derivatives of Kdg and their 3-bromo and 3-deuterio analogues, were also prepared from D-glucono-1,5-lactone³¹⁹ via the 2-enonolactone.⁹⁸

Fourthly, biotransformations have been used for the synthesis of 3-deoxy-2-glyculosonic acids, using whole cells or purified enzymes. For instance, 3-deoxy-D-*arabino*-heptulosonic acid (DAH) and its 7-phosphate (DAHP, **122**) have been produced directly from D-glucose by mutants of *E. coli* JB-5, that lack dehydroquinase synthase, the enzyme that converts DAHP into the cyclic intermediate dehydroquinic acid (DHQ, Scheme 14). Both DAH and DAHP are secreted into the medium. The dephosphorylated product could be generated *in vivo* by a phosphatase acting on DAHP.³¹²

Synthesis using immobilized enzymes has also been applied to the preparation of DAHP.³²⁰ The 7-phosphonate of DAH, having a C-P

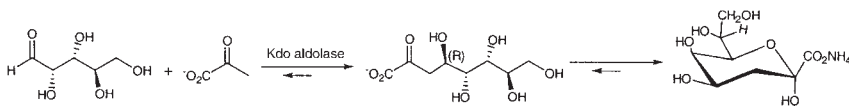


SCHEME 14

linkage, has been prepared as a putative inhibitor of the enzyme dehydroquinate synthetase. This phosphonate analogue of DAHP has the advantage that it is not hydrolyzed by phosphatases.

3-Deoxy-D-*erythro*-hex-2-ulosonic acid 6-phosphate (KDPG), an intermediate in glucose metabolism, is synthesized by a strain of *Alcaligenes eutrophus*, lacking KDPG-aldolase activity. Pyruvate and gluconate are used as carbon sources, and KDPG was isolated from the culture supernatants in 78% yields with respect to the gluconate consumed.³²¹

3-Deoxy-2-glyculosonic acids have been synthesized by using different aldolases with pyruvate as the nucleophile.³²² 3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) was obtained from D-arabinose and pyruvate in 67% yield by using Kdo aldolase (EC 4.1.2.23) from *Aureobacterium barkerei* strain Kdo-37-2 (Scheme 15). The enzyme accept trioses, tetroses, pentoses, and hexoses as substrates, especially those having the *R* configuration at C-3. The following 3-deoxy-2-glyculosonic acids have also been prepared: 3-deoxy-D-*arabino*-2-heptulosonic acid (D-DAH), "2-keto-3-deoxy-L-gluconic acid" (L-Kdg), and 3-deoxy-L-*glycero*-L-*galacto*-nonulosonic acid (L-Kdn). The substituent on the 2-position has little effect on the aldol reaction.³²³



SCHEME 15

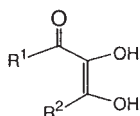
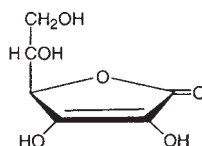
5. L-Ascorbic Acids

L-Ascorbic acids are a class of compounds known as *aci*-reductones (137), which are enolic lactones of 2- and 3-glyculosonic acids. They are illustrated by the formula of the most important member of the

group, *L-threo*-hex-2-enono-1,4-lactone (**138**), also known as vitamin C, *L-xylo*-ascorbic acid, or simply *L*-ascorbic acid. The common terms used for the *L*-ascorbic acids are based on the configuration of the glycosonic acid actually or hypothetically used in its preparation.

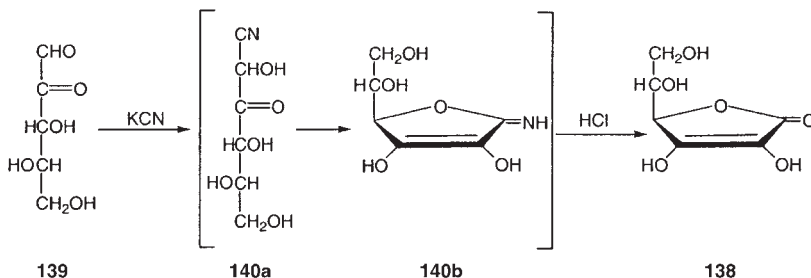
Of the many analogues of vitamin C that have been synthesized, only those having the lactone ring on the right of the formula when written according to the Fischer convention display antiscorbutic activity. The 6-deoxy analogue of **138** has about one-third of the activity of the natural vitamin, but a 2-amino-2,6-dideoxy analogue and a seven-carbon analogue of **138** (*L-rhamno*-ascorbic acid) exhibit rather high activities; however, the C-5 epimer of **138** (*D-arabino*-ascorbic acid) has much lower activity.

Reviews on the preparation and properties of *L*-ascorbic acid have been published.^{274,324}

**137****138**

a. Synthesis.—The *L*-ascorbic acids have generally been synthesized by two main routes: by cyanohydrin synthesis from glycos-2-uloses, and by enolization and lactonization of glycosonic acids or esters.

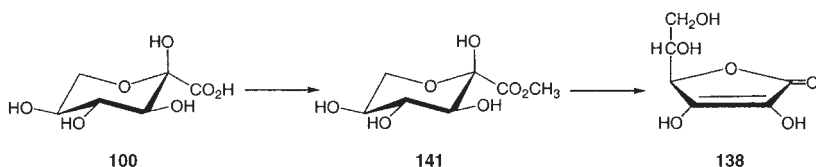
The addition of cyanide to a glycos-2-ulose has been used for the preparation of many ascorbic acids, including the first synthesis of **138** (see Ref. 274), starting from *L-threo*-pentos-2-ulose (**139**). In this synthesis, the nitrile **140a** undergoes immediate enolization and ring closure, to form the iminolactone **140b**, which can be isolated crystalline; **140** is readily converted by dilute acid into **138** (total yield, ~40%). The starting compound **139** can be obtained from *L*-xylose by oxidation with $\text{Cu}(\text{OAc})_2$ in aqueous methanol.³²⁶



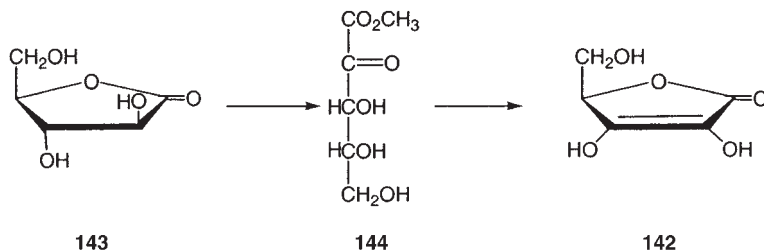
This route has been used and refined, for the synthesis of $[1-^{13}\text{C}]$ - and $[2-^{13}\text{C}]$ -ascorbic acid, useful for *in vivo* investigations of the biological role of vitamin C.³²⁶

The second approach, the simultaneous enolization and lactonization of 2-glycosulonic acids or esters, is generally the method of choice for the preparation of L-ascorbic acids, provided that the required 2-glycosulonic acid is an accessible starting material.

The base-catalyzed cyclization of methyl L-*xylo*-2-hexulosonate (**141**) to L-ascorbic acid under different conditions has been extensively used (see Ref. 274). The starting compound L-*xylo*-2-hexulosonic acid (**100**) can be obtained in good yield from L-sorbose (**97**).

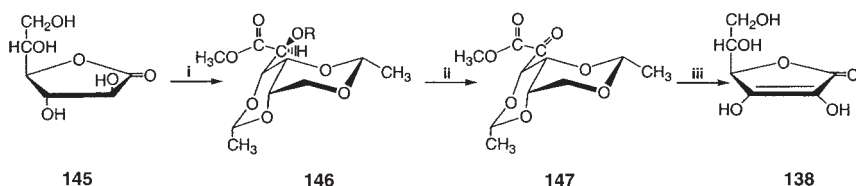


D-Erythroascorbic acid (D-*glycero*-2-pentenono-1,4-lactone, **142**), was prepared from D-glucose by degradative oxidation to potassium D-arabinonate, which was acidified and lactonized. The lactone **143** was converted in one step into the 2-keto methyl ester **144**, which finally was tautomerized in hot methanolic sodium acetate, affording D-erythroascorbic acid (**142**) as a crystalline solid.³²⁸



Acid-catalyzed cyclization has also been applied to the preparation of L-ascorbic acid, starting from the free acid (**100**) or from the precursor 2,3:4,6-di-*O*-isopropylidene-L-*xylo*-2-hexulofuranosic acid (**99**). A summary of the methods prior to 1980 is given in Ref. 274.

An interesting approach for the synthesis of L-ascorbic acid uses L-galactono-1,4-lactone, a byproduct of the sugar industry. It involves opening of L-galactono-1,4-lactone (**145**) by reaction with a methanolic solution of acetaldehyde. The resultant methyl 3,5:4,6-di-*O*-ethylidene-galactonate (**146**) was oxidized with $\text{RuO}_2\text{-Ca}(\text{OCl})_2$, leading to the 2-ketoester **147**, which under acidic conditions provided vitamin C.³²⁹



i, CH_3CHO , MeOH/HCl ; ii, $\text{RuO}_2/\text{Ca}(\text{OCl})_2$; iii, HCl/EtOH , CH_2Cl_2

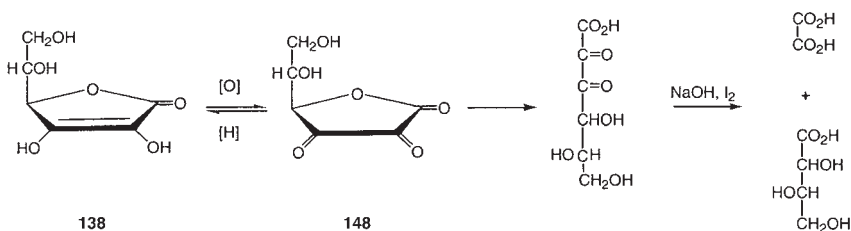
Anodic oxidation of a 1,3:2,4-diacetal of D-glucitol led to the 3,5:4,6-diacetal of “2-keto-L-gulonic acid,” which gave L-ascorbic acid directly on hydrolysis.³³⁰

b. General Properties and Reactions.—The enediol grouping in these acids is the basis of their acidity, reducing properties, and instability in alkaline solution. Ascorbate ions are much more nucleophilic than expected from their pK_a values, because of the acidity of the C-2 hydroxyl group.³³¹

Ascorbic acids reduce Fehling solution in the cold, and react with ferric chloride to produce the violet color typical of enolic compounds. They are readily oxidized reversibly to their primary oxidation products, 2,3-glycoidulosono-1,4-lactones (commonly known as dehydroascorbic acids **148**, Scheme 16), by such mild oxidizing agents as aqueous iodine. Titration with such oxidants constitutes a quantitative method for distinguishing ascorbic acids from 2-glyculosonic acids.

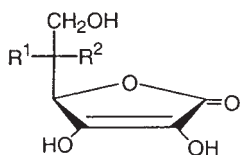
The action of boiling 12% hydrogen chloride converts ascorbic acids into 2-furaldehyde in high yield.³³²

Brenner *et al.*³³³ studied the isomerization of ascorbic acids. Epimerization at C-4 occurs in boiling 50% aqueous methanol containing potassium hydroxide, and an approximately equal mixture of epimers was obtained after 16–24 h. The rare *L-erythro*- and *D-threo* isomers of ascorbic acid were isolated as solids by fractional recrystallization of epimerized mixtures



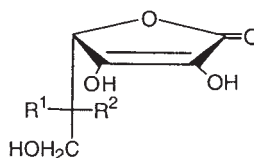
SCHEME 16

obtained from the more readily available *L*-threo- (**138**) and *D*-erythro-hex-2-enono-1,4-lactones. Benzyl ether and benzylidene acetal derivatives of *L*-ascorbic acid (**138**), and *D*-isoascorbic acid (*D*-arabinoascorbic acid, **149**), have been found to epimerize partly to the corresponding derivatives of *L*-isoascorbic acid (**150**) or *D*-ascorbic acid (**151**), respectively, on treatment with triisobutylaluminium (TRIBAL).³³⁴



138 *L*-ascorbic acid $R^1 = H, R^2 = OH$

149 *D*-isoascorbic acid $R^1 = OH, R^2 = H$



150 *L*-isoascorbic acid $R^1 = OH, R^2 = H$

151 *D*-ascorbic acid $R^1 = H, R^2 = OH$

c. Vitamin C (*L*-Ascorbic Acid, *L*-threo-Hex-2-enono-1,4-lactone, **138**).—

Vitamin C (*L*-ascorbic acid) was first isolated as a strongly reducing crystalline substance, originally termed “hexuronic acid,” by Szent-Gyorgyi in 1928 from adrenal glands, oranges, and cabbages. *L*-Ascorbic acid was later shown to possess the antiscorbutic activity long known in lemon juice, from which it was later isolated. The vitamin is widely distributed in Nature; in addition to citrus fruits, other particularly rich sources include blackcurrants, paprika, and rose hips.

The structure of **138** was elucidated, shortly after its isolation, in extensive contributions by many groups. Several important discoveries relating to its constitution were reported in 1933, the same year in which the first successful synthesis was described (see Refs. 274, 324). Thus, the group at the University of Birmingham³³⁵ found that the primary oxidation product of **138**, the 2,3-diulosono-lactone **148** (dehydroascorbic acid), could be quantitatively oxidized by sodium hypoiodite to generate oxalic acid and *L*-threonic acid (Scheme 16), which was identified as the crystalline tri-*O*-methyl-*L*-threonamide. These results established the stereochemical relationship between **138** and *L*-gulonic (and *L*-idonic) acid. The work that provided support for the structure of *L*-ascorbic acid has been summarized in several reviews.^{274,336}

The equilibrium between **138** and the reversible oxidation product **148** is vital to plant and animal life; it apparently functions to mediate the transfer of hydrogen atoms. Solutions of *L*-ascorbic acid, which is readily oxidized, are more sensitive to alkalis than to acids, and the rates of oxidation are lower under slightly acid conditions. The stability of **138**

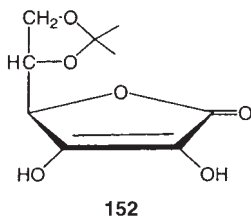
is very important in the food industry. Oxidation in milk is accelerated by copper and by sunlight. Enzymes in plant cells, including a copper-containing L-ascorbic acid oxidase, degrade vitamin C when plant tissues are damaged.

Most plants and animals (except man, monkey, and guinea pig) seem able to synthesize the vitamin. Biosynthesis of L-ascorbate occurs by different pathways in plants and animals. Yeast contain a five-carbon analogue, D-erythroascorbate (**142**).

In animals, UDP-D-glucuronic acid is the precursor; it loses UDP and the D-glucuronic acid/D-glucuronolactone is reduced at C-1, forming L-gulonic acid/L-gulono-1,4-lactone. The lactone is oxidized by microsomal L-gulono-1,4-lactone oxidase to ascorbate. This enzyme is not expressed in primates, as they have lost biosynthetic capacity for ascorbate.

Plants form ascorbate from GDP-mannose via GDP-L-galactose, L-galactose and L-galactono-1,4-lactone. The latter is oxidized to L-ascorbic acid by a mitochondrial L-galactono-1,4-lactone dehydrogenase, using cytochrome *c* as electron acceptor. The biosynthesis of L-ascorbic acid has been reviewed.³³⁷

Analysis of vitamin C has been the topic of numerous papers. Most of the methods analyze L-ascorbic acid by HPLC, before and after reduction of the dehydroascorbic acid present.³³⁸ The concentration of the dehydroascorbic acid is calculated by subtraction. A later work describes a method, which combines iodometry with a voltammetric technique to detect the end-point of the titration.³³⁹ The results are comparable to those obtained by HPLC and can be applied to vegetable and fruit samples.



The 5,6-*O*-isopropylidene acetal (**152**) of L-ascorbic acid has been prepared,³⁴⁰ and von Schuching and Frye³⁴¹ prepared the corresponding cyclohexylidene acetal. These compounds were found to be more resistant than L-ascorbic acid toward oxidation, and the parent acid can be readily regenerated by acid hydrolysis. The derivative was used in the synthesis of ¹⁴C-labeled vitamin C. The C-2 and C-3 enols of L-ascorbic acid or its acetone derivative (**152**) can be readily methylated with diazomethane, yielding the corresponding dimethoxy analogues.

The high functionality of vitamin C offers the possibilities for a large number of modifications. The understanding of the chemistry and the biochemistry of ascorbic acid and its derivatives has been helpful in the development of pharmacologically important agents having optimized activities. The chemical modification of the hydroxyl groups of vitamin C is of particular interest, and numerous derivatives have been reported, some of which showed important pharmacological properties.

The well-known susceptibility of vitamin C to thermal and oxidative degradation has focused interest in derivatives of increased stability. In general, partial modification of the enediol system leads to two isomers, both of which have markedly lower reducing power and are therefore stabilized against oxidation. However, vitamin C activities tend to decrease in these substituted derivatives.

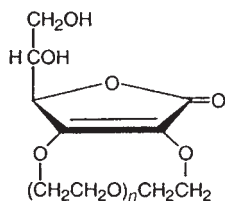
O-Sulfation of **138** by pyridine-sulfur trioxide occurs exclusively at O-2,³⁴² whereas phosphorylation affords several products.^{343,344}

Jackson and Jones³⁴⁵ reported the alkylation of L-ascorbic acid with benzyl chloride, which produced a 2-*C*-benzyl-3-hexulosonolactone and 3-*O*-benzyl-L-*threo*-hex-2-enono-1,4-lactone.

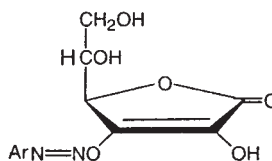
2-*C*-Alkylated derivatives have shown immunostimulant properties, and 2-*O*- and -3-*O*-alkylated lipid-soluble derivatives are known to protect against the lipid peroxidation of biomembranes.²⁵⁰

Many efforts have been directed to the regioselective substitution of either HO-2 or -3 and to stereocontrolled addition reactions to the double bond. The acylation and alkylation of such hydroxyl groups is fairly sensitive to the reaction conditions. It is reported that alkylation of ascorbic acid in solvents of high dielectric constant favors 2-*C*-alkylation when powerful alkylation agents were employed.³⁴⁶

Alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid (**152**) with alkyl halides in *N,N*-dimethylformamide affords 2,3-di-*O*-alkyl derivatives of L-ascorbic acid.³⁴⁷ Likewise, crown ether-type derivatives (**153**) may be obtained by interaction with the appropriate ditosylate and K_2CO_3 in *N,N*-dimethylformamide. The reaction was unsuccessful with $n = 2$.³⁴⁸



153 $n = 1, 3, 4$

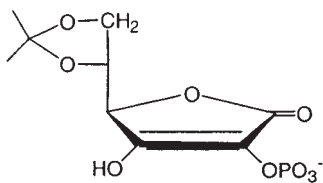


154

Selective alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid (**152**) at O-3 has been performed with K_2CO_3 -acetone-alkyl halides. With an excess of alkyl halide, the 2,3-di-*O*-alkylated derivatives could be obtained, but by stepwise alkylation different alkyl moieties could be introduced at O-3 and O-2.³⁴⁹

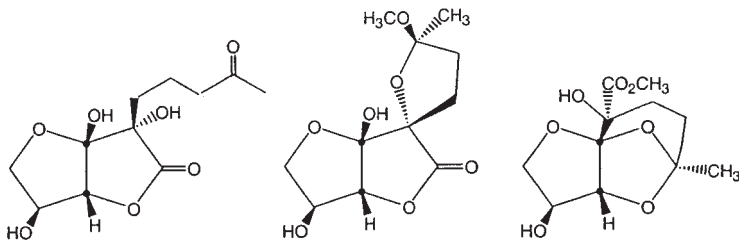
Treatment of ascorbic acid with *p*-nitrobenzenediazonium tetrafluoroborate in aqueous phosphate-buffered solution at pH 7 led to the stable 3-*O*-arenediazoascorbic acid **154**, instead of a reaction of electron transfer. The diazo ether derivatives are stable over a wide range of pH and are resistant to nucleophilic displacement.³⁵⁰

Selective phosphorylation of 5,6-*O*-isopropylidene D-erythorbic acid (D-*erythro*-hex-2-enono-1,4-lactone), the 5-epimer of L-ascorbic acid, was performed with phosphoryl chloride at high pH in the presence of pyridine. D-Erythorbate 2-phosphate (**155**) is obtained as the crystalline magnesium or cyclohexylammonium salts following removal of the 5,6-acetal.³⁵¹

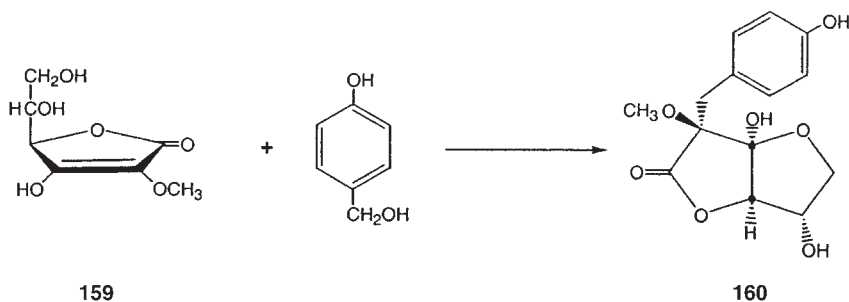
**155**

Enzymic transglycosylation, with maltose as the glycosyl donor, can be used to make 2-*O*- α -D-glucopyranosyl-L-ascorbic acid, used as a stable storage form of ascorbate in commercial formulations.³⁵²

Condensation of ascorbic acid with methyl vinyl ketone afforded the ketobutyrolactone **156** ("KBBL"), which has immunostimulant activity. Upon treatment with methanol in acid **156** rearranges to **157** and **158**.³⁵³

**156****157****158**

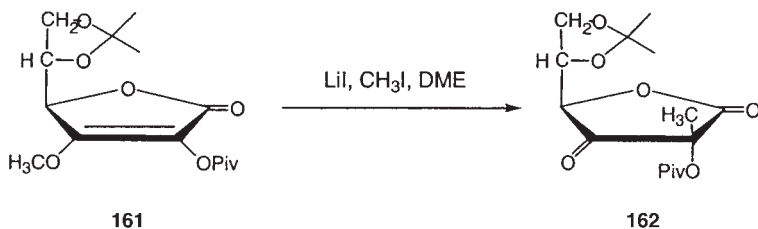
By benzylation of 2-*O*-methyl-L-ascorbic acid **159** at C-2, according to Scheme 17, the stereospecific construction of marine algae metabolite delesserrine (**160**) was achieved.³⁵⁴



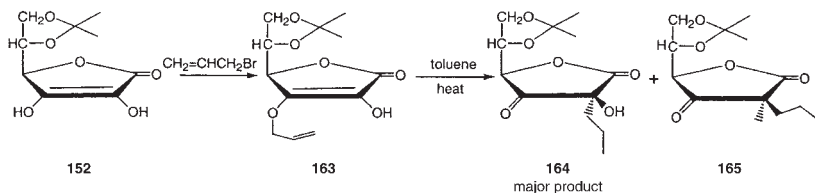
SCHEME 17

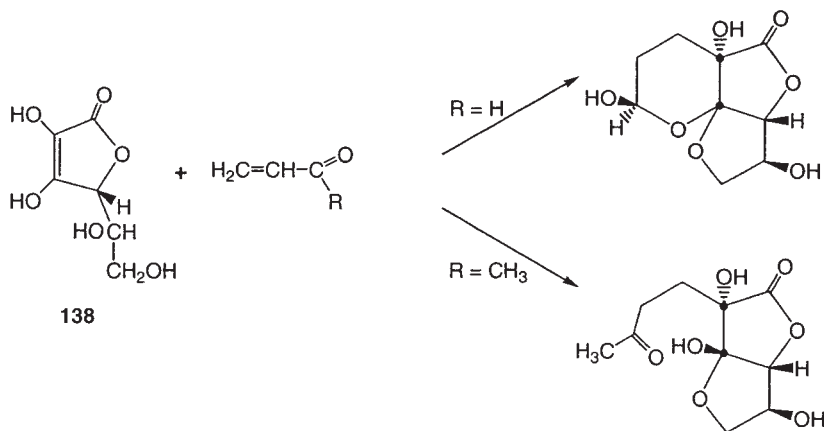
A good route to 2-*C*-allyl (and hence by reduction, *C*-alkyl) derivatives of ascorbic acid involves the interaction of L-ascorbic acid with allyl acetates or allyl carbonates in the presence of Pd(0) catalyst.³⁵⁵

Treatment of L-ascorbic derivative **161** with lithium iodide and methyl iodide in 1,2-dimethoxyethane gave the *C*-methylation product **162** with high diastereoselectivity, and similar results were found with the equivalent D-isoascorbic derivative.³⁵⁶



During the course of studies on the allylation of 5,6-*O*-isopropylidene-L-ascorbic acid (**152**), it was shown that the 3-*O*-allyl derivative **163** was formed in high yield by reaction of **152** with allyl bromide and K₂CO₃ in dimethyl sulfoxide at room temperature.³⁵⁷ It was later shown that the 3-*O*-allyl derivative (**163**) can rearrange to the thermodynamically more stable 2-*C*-allylated products (**164**, **165**) in a time- and temperature-dependent manner.³⁵⁸

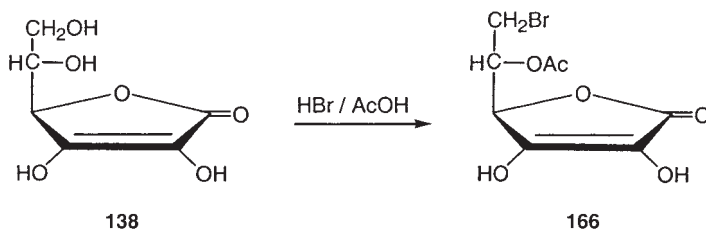




SCHEME 18

L-Ascorbic acid reacts as a Michael-type carbanion donor with α,β -unsaturated aldehydes and ketones. The way in which the adduct is stabilized depends on whether an aldehyde or a ketone is involved (Scheme 18).³⁵⁹

A reaction, that does not involve the enediol takes place on halogenation. Treatment of **138** with hydrogen bromide–acetic acid affords 5-*O*-acetyl-6-deoxy-L-ascorbic acid (**166**).³⁶⁰ Compound **166** was used for the synthesis of 6-substituted derivatives of **138**, via the 5,6-anhydro derivative.³⁶¹



In connection with the antioxidant properties of L-ascorbic acid and its stability, many kinetic and mechanistic studies have been performed. For instance, it has been shown a role as a radical scavenger in the autooxidation of methyl linoleate, and its synergistic effect when used with vitamin E.³⁶² The photooxidation,³⁶³ superoxide-mediated oxidations,³⁶⁴ reactions with radicals,³⁶⁵ and the influence of other agents, including ultrasound and γ -rays,³⁶⁶ have been reported.

L-Ascorbic acid serves as a reductant for several important enzymatic biotransformations. These characteristic biological activities result from its enediol structure, which confers a strong electron-donating ability. In addition, there is considerable evidence that biological antioxidants, including ascorbic acid, play an important role in the prevention of a large number of chronic diseases such as cancer, cerebral apoplexy, diabetes, myocardial damage, and AIDS.^{367,368}

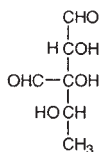
The long-standing interest in the properties of L-ascorbic acid is manifested by the fact that 1146 references related to vitamin C are listed for year 2000 in the PUB MED index in the Internet. The most popular use of L-ascorbic acid is for prevention and treatment of the common cold, but this role remains controversial. In a recent review, the authors conclude that the long-term daily supplementation with large doses of vitamin C does not appear to prevent colds, but there is a modest therapeutic effect on the duration of cold symptoms.³⁶⁹

III. NEUTRAL OXIDATION PRODUCTS

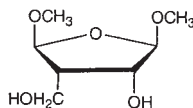
This section deals with those neutral carbohydrates having two carbonyl groups, either free or substituted, present in the same carbon chain. Some of these compounds are prepared by cleaving exocyclic or inositol α -glycol groups. The neutral dicarbonyl compounds are divided into three categories: (1) dialdehydes (dialdoses), (2) ketoaldehydes (glycosuloses), and (3) diketo compounds (glycodiuloses). A review by Theander³⁷⁰ contains detailed information about the various dicarbonyl carbohydrates known up to 1962.

1. Dialdoses

Several compounds of this type, formally derived from aldoses by oxidation of the terminal $-\text{CH}_2\text{OH}$ group to $-\text{CHO}$, have been prepared. Dialdoses arise as intermediates in structural studies, but they are also valuable starting materials for synthetic conversions, in particular for natural-product synthesis. A branched-chain dialdose, streptose (**167**), occurs as a component of the antibiotic streptomycin. The structure of streptose was elucidated after extensive investigations of its derivatives and transformation products.³⁷¹ The 2,5-dimethoxytetrahydrofuran fulvanol (**168**), an analogue of apiose, has been isolated from the plant *Hemerocallis fulva*.³⁷²



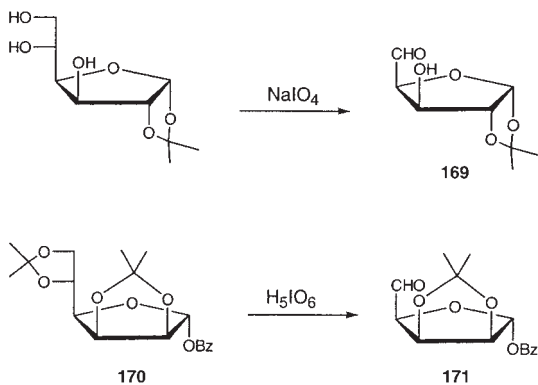
167



168

a. Preparation.—With a few exceptions, the general approaches for the preparation of dialdoses and their derivatives have employed either oxidative cleavage of α -glycols; controlled oxidation of one, or two, primary alcoholic groups; or reduction of one, or two, carboxyl groups.

1,2-*O*-Isopropylidene- α -D-xylo-pentodialdo-1,4-furanose (**169**), which has been used for many syntheses, was prepared through oxidation of 1,2-*O*-isopropylidene- α -D-glucofuranose with periodate.³⁷³ Cleavage of partially protected aldohexose dithioacetals by sodium periodate leads to pentodialdose derivatives.³⁷⁴ Periodic acid hydrate in ether has been used for selective cleavage of terminal *O*-isopropylidene groups, and thence cleavage of the released diol in a one-pot process. Thus, the di-*O*-isopropylidene-D-mannose derivative **170** gave the pentodialdose derivative **171**. This method is successfully applicable to substrates containing a variety of protecting groups [acetate, methoxymethyl (MOM), benzoyl (BzO), *tert*-butyldimethylsilyl (TBDMS)] with high yields.³⁷⁵

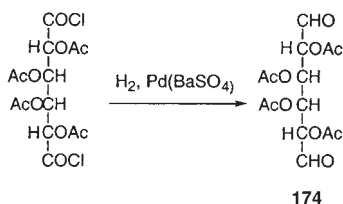
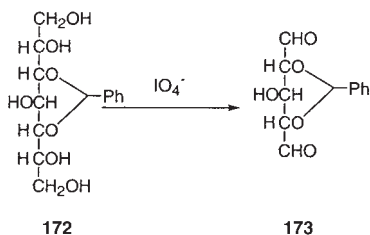


Methyl pentodialdofuranosides³⁷⁶ and methyl hexodialdopyranosides³⁷⁷ were prepared in quite good yields by equimolar periodate oxidation of the exocyclic α -glycol grouping of the next higher homologous methyl glycoside.

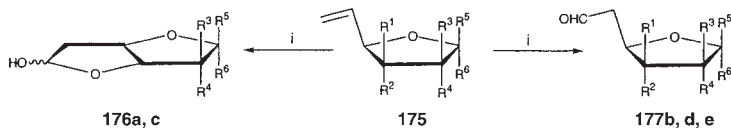
Hexodialdoses have also been obtained by α -glycol cleavage in suitably substituted alditols. The 3,5-benzylidene acetal (**172**) of

D-*glycero*-D-*gulo*-heptitol afforded the xylodialdose derivative **173** by oxidation with sodium metaperiodate.³⁷⁸

2,3,4,5-Tetra-*O*-acetyl-*galacto*-hexodialdose (**174**) was prepared by Rosenmund reduction of the dichloride of tetra-*O*-acetylgalactaric acid.³⁷⁹



Pd(II)Cl₂-mediated oxidation (Wacker reaction) of protected 3-hydroxy-4-vinylfuranosides yields aldehydes. When the 3-hydroxyl group is free and in *cis* relation (**175a,c**) to the exocyclic vinyl group, the products formed were lactols (**176a,c**). If the 3-hydroxyl group is free and in *trans* orientation (**175e**), the aldehyde **177e** was obtained. It was also observed that when the 3-hydroxyl group was protected (**175b,d**) Wacker oxidation led to the aldehydes (**177b,d**).³⁸⁰



a) $\text{R}^1 = \text{R}^3 = \text{OH}$, $\text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$, $\text{R}^6 = \text{OBn}$

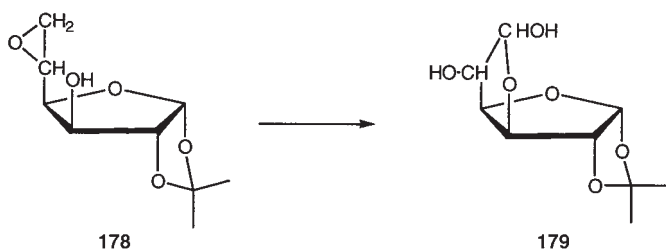
b) $\text{R}^1 = \text{R}^3 = \text{O}$ (cyclic acetal), $\text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$, $\text{R}^6 = \text{OBn}$

c) $\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{OTBDMS}$, $\text{R}^5/\text{R}^6 = \alpha = \beta = \text{OCH}_3$

d) $\text{R}^1 = \text{OBz}$, $\text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{OTBDMS}$, $\text{R}^5/\text{R}^6 = \alpha = \beta = \text{OCH}_3$

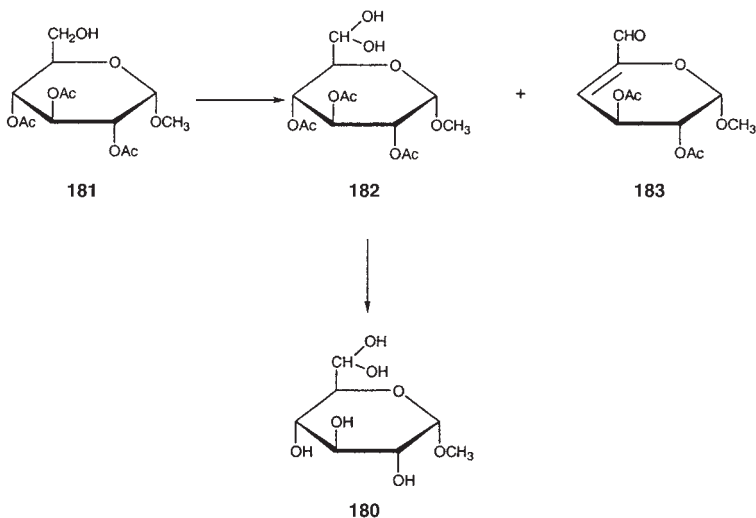
e) $\text{R}^1 = \text{R}^3 = \text{R}^5 = \text{H}$, $\text{R}^2 = \text{OH}$, $\text{R}^4 = \text{R}^6 = \text{O}$ (cyclic acetal)

Crystalline 1,2-*O*-isopropylidene- α -D-*gluco*-hexodialdo-1,4:6,3-difuranose (**179**) has been prepared³⁸¹ via dimethyl sulfoxide oxidation of **178**, and by chromic acid oxidation of 1,2-*O*-isopropylidene- α -D-glucofuranose.³⁸²



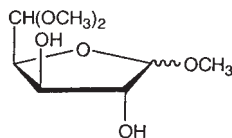
Horton *et al.*³⁸³ used dimethyl sulfoxide oxidation (Pfitzner–Moffatt reagent) for the preparation of 1,2:3,4-di-*O*-isopropylidene- α -D-galacto-hexodialdo-1,5-pyranose from the corresponding D-galactose derivative. Direct oxidation of the primary hydroxyl group in methyl hexopyranosides having unprotected secondary hydroxyl groups generally gives only low yields of ω -aldehyde compounds.³⁷⁰

Methyl α -D-*gluco*-hexodialdoside 6-hydrate (**180**) and the β -D-*gluco* and α -D-*galacto* isomers were prepared by oxidation at C-6 of suitable derivatives. Starting from **181** the Swern reagent (dimethyl sulfoxide, trifluoroacetic anhydride, triethylamine) gave mixtures of the desired aldehyde **182** and the unsaturated aldehyde **183**. A similar result was obtained with a Moffatt reagent formulation using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride. However, the use of *N,N'*-diisopropylcarbodiimide with dimethyl sulfoxide–pyridinium trifluoroacetate gave the desired aldehyde trapped as the imidazolidine derivative, in nearly quantitative yield. Deacylation led to the dialdehyde **180** in good yield.³⁸⁴ ¹³C NMR spectra showed that C-6 is hydrated.

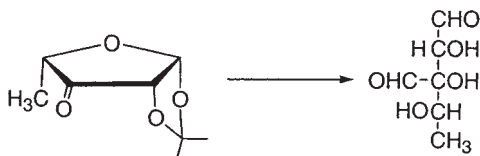


Photolysis of primary azido derivatives of sugar glycosides has been successfully employed for the synthesis of dialdose derivatives. The nonaqueous method³⁸⁵ was modified by performing photolysis of the unprotected azides in acidic water solution, which gave high yields of the corresponding dialdoside hydrates.³⁸⁴

Photolysis of D-glucose in methanol containing titanium(IV) chloride gave the D-*xyl*o-pentodialdose glycoside acetal **184** in 60% yield; D-galactose behaved similarly.³⁸⁶

**184**

A chain-elongation reaction was used for the synthesis of streptose (**167**) starting from 5-deoxy-1,2-*O*-isopropylidene- β -L-*threo*-pentofuranos-3-ulose (**185**).³⁸⁷

**185****167**

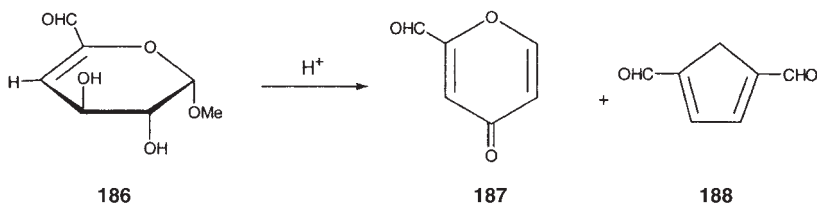
Galactose oxidase (EC 1.1.3.9), which catalyzes the oxidation of D-galactose (and derivatives) to D-*galacto*-hexodialdose (and derivatives), is useful for analytical determinations,³⁸⁸ but is not an efficient method for large-scale preparation of methyl D-*galacto*-hexodialdo-1,5-pyranosides. The β anomer of the latter was characterized as a dimeric hexaacetate.³⁸⁹

b. Properties and Reactions.—The aldehyde group at C-6 of dialdoses is strongly electrophilic and very reactive. Such compounds readily undergo dimer, hemiacetal, acetal, and dithioacetal formation. Dialdoses and their derivatives that contain one or two unsubstituted carbonyl group(s) generally appear as multiple spots on chromatograms, and undergo mutarotation in aqueous solution;³⁷⁰ these phenomena reveal that an equilibrium is established between different cyclic and acyclic forms of dialdoses. The rates at which these equilibria are established approximate those for conversions between lactones and the free acid form of carbohydrate acids. The different components of the equilibrium may be isolated by column chromatography on cellulose or carbon; however, each

reverts to the same equilibrium mixture after a few days. Many forms are possible, depending, among other things, on the number of hydroxyl groups available for ring formation; crystalline dialdose derivatives spontaneously adopt many different (dimeric, hemiacetal, and polycyclic) forms, and evidence has also been found for free aldehyde forms, hydrates, and hemialdals.³⁷⁰

Methyl hexodialdopyranosides (including methyl 6,6'-dialdehydro- β -cellobioside),³⁹⁰ readily undergo β -elimination at C-4 at pH 3 and above.³⁹¹

The unsaturated hexodialdopyranosides formed are very readily transformed by either alkaline or acid treatment into brown, polymerized products. Acid treatment of **186**, the β -elimination product of methyl α -D-*gluco*-hexodialdo-1,5-pyranoside, produced the reactive intermediates **187** and **188**.³⁹¹ The 2,3-diacetate of **186** was obtained by Perlin *et al.* by an oxidation- β -elimination reaction.³⁹²



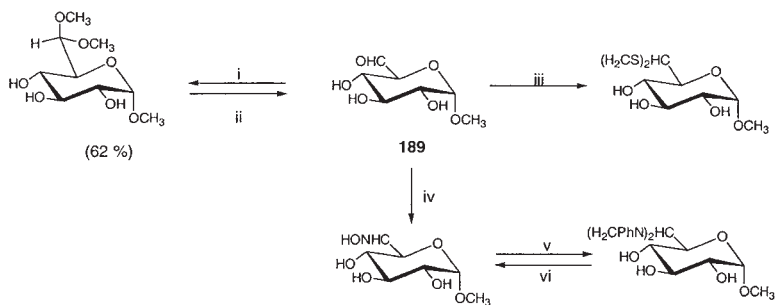
Acyclic dialdoses, and derivatives having one free aldehyde group, generally exhibit properties of typical acetylated aldehyde sugars and aliphatic aldehydes rather than of typical monosaccharides; thus, they give a positive Schiff test and exhibit strong electrophoretic migration in the presence of hydrogensulfite.

Ballou and Fischer³⁹³ treated D-*manno*-hexodialdose and its 2,3:4,5-di-*O*-isopropylidene derivative with methanol under Fischer glycosidation conditions, and obtained not only glycosides, but also some dimethyl acetals, and a crystalline difuranoside (probably the α,α anomer) was obtained in 20% yield.

The following reactions have been performed with the dialdehyde derivative **189** (Scheme 19).³⁸⁴

An important transformation of dialdoses is the chain extension to homologous products by condensations performed on the aldehyde group. When asymmetric induction occurs, this transformation is extremely valuable for the stereocontrolled synthesis of higher sugars.

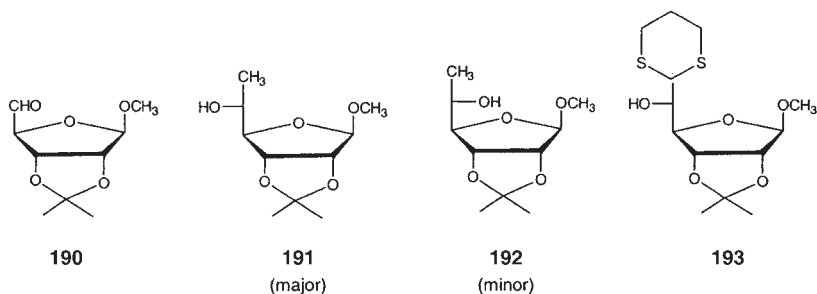
Methyl 2,3-*O*-isopropylidene- β -D-ribopentodialdo-1,4-furanoside (**190**) undergoes interesting changes in stereoselectivity on reaction with different reagents. Whereas methyllithium and methylmagnesium iodide give the



i, CH_3OH , H^+ , heat, 16 h; H_2O , pH 2, 40-45 $^\circ\text{C}$; iii, $(\text{CH}_2\text{SH})_2$, CH_3OH , H^+ , heat; iv, CH_3OH , KCO_3H , $\text{NH}_2\text{OH}\cdot\text{HCl}$; v, $(\text{PhNHCH}_2)_2$, CH_3OH , pH 5; vi, Amberlite(H^+), acetone- H_2O .

SCHEME 19

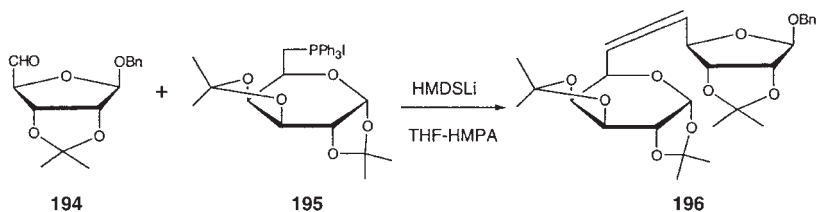
β -D-*allo*- and α -D-*talo*-adducts **191** and **192** in $\sim 3:1$ ratio; 2-lithio-1,3-dithiane affords, almost exclusively, the alloside **193**.³⁹⁴



Grosheintz and Fischer³⁹⁵ prepared 6-deoxy-6-nitro derivatives of D-glucose and L-idose by condensation of nitromethane with 1,2-*O*-isopropylidene- α -D-*xylo*-pentodialdo-1,4-furanose (**170**), as intermediates in a synthesis of some nitrocyclitol derivatives. Lichtenthaler³⁹⁶ described a synthesis of ^{14}C -labeled *myo*-inositol starting from *xylo*-pentodialdose. D-[6- ^{14}C]Glucose, L-[6- ^{14}C]idose, and the corresponding labeled glycuronic acids, have been prepared from **170** via the cyanohydrin reaction, a method that has been improved upon through the extensive studies of Schaffer and Isbell.³⁹⁷

Schaffer³⁹⁸ described a synthesis of L-apiose by reaction of **170** with formaldehyde, and Horton *et al.*³⁷³ developed a method for extension of sugar chains through ethynylation of **170** and other aldehydo compounds by the Grignard reaction.

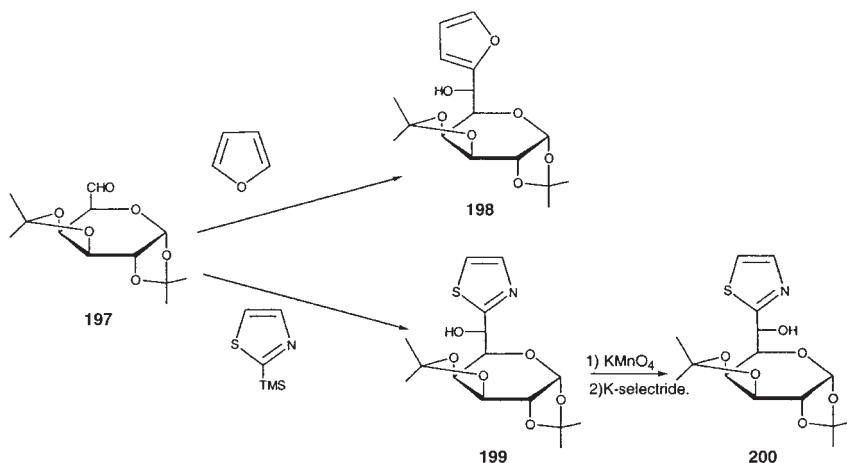
Other alternatives for chain extension have been developed. Wittig condensation between the dialdose derivative **194** and the (PPh₃I) mono-saccharide derivative **195** occurs with complete stereoselectivity, forming a *cis* linkage. Compound **196** is the precursor of a deaminotunicamine derivative.³⁹⁹



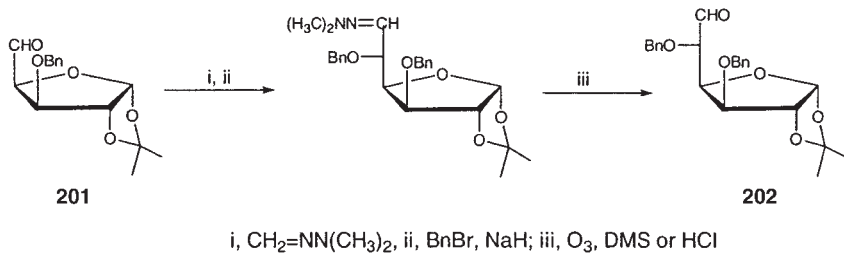
The aldehydes at C-6 of dialdoses have also been used as dienophiles in hetero-Diels–Alder reactions.⁴⁰⁰

Reaction of several dialdose derivatives, for example **197**, with furan or 2-methylfuran gave, in the presence of chloroacetic acid, condensation products with high stereoselectivity. The (*S*) configuration was assigned to the major diastereoisomer **198**.⁴⁰¹ The thiazole adduct (**199**) obtained from aldehyde **197** and 2-trimethylsilylthiazole can be converted to the 6-epimer (**200**) by an oxidation–reduction sequence (Scheme 20).⁴⁰²

The 1,5-dialdose derivative **201** has been chain-extended to the 1,6-dialdose derivative **202**, by stereospecific addition of formaldehyde dimethylhydrazone, according to Scheme 21.⁴⁰³

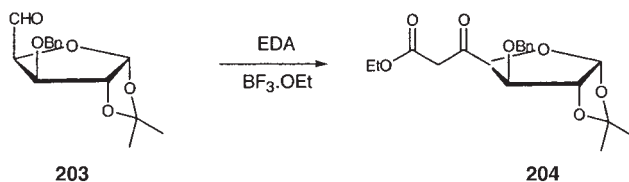


SCHEME 20



SCHEME 21

A direct method for two-carbon sugar homologation of dialdoses leads to sugar β -ketoesters. Thus, reaction of dialdose derivative **203** with ethyl diazoacetate in the presence of BF₃ etherate affords the β -ketoester **204**.⁴⁰⁴



2. Glycosuloses

These compounds are formally derived from aldoses by oxidation of a secondary hydroxyl group to a ketone group. The well-known aldoses-2-uloses (usually termed simply *aldosuloses* or *osones* in former usage) have long been known in the form of their bis(hydrazone) derivatives, the osazones. Deoxyaldosuloses have been implicated as intermediates in a variety of degradation reactions. Aldoses-3-, -4-, and -5-uloses have been prepared, principally as intermediates for synthesis.

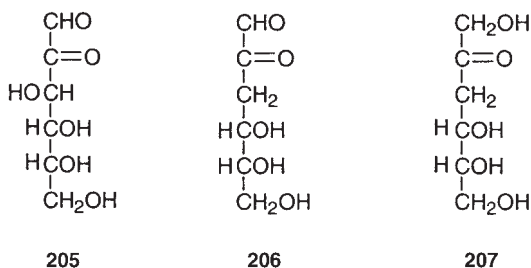
a. Occurrence.—Saponins from the leaves of *Gymnena sylvestre* were found to contain *O*- β -D-*arabino*-hexos-2-ulopyranosyl moieties.⁴⁰⁵ A double-linked 4,6-dideoxy-D-*threo*-hexos-2-ulose residue was identified in the cardenolide isolated from *Asclepias curassavica* stems.⁴⁰⁶

β -D-*ribo*-Hexopyranosid-3-ulose has been found in cardenolide glycosides of air-dried leaves of two *Cerbera* species,⁴⁰⁷ and in iridoid glycosides from *Penstemon* species leaves.^{408,409}

It has been suggested that D-*arabino*-hexos-2-ulose (**205**) is formed by metal-catalyzed autooxidation of glucose.⁴¹⁰

The degradation of Amadori compounds, important in the browning reaction occurring during food processing, has been studied with

“fructose β -alanine” (“FA”) as a model compound. FA was degraded in aqueous solution in the presence of copper ion to D-*arabino*-hexos-2-ulose (**205**) and β -alanine.⁴¹¹



The 3-deoxyhexos-2-uloses, which had long been hypothesized as intermediates in many important degradation reactions of carbohydrates, have been isolated and studied,⁴¹² in particular, 3-deoxy-D-*erythro*-hexos-2-ulose “3-deoxyglucosone” (**206**), which is found in higher concentrations in diabetic animals.⁴¹³ In mammals, a significant proportion of **206** is reduced to form 3-deoxy-D-*erythro*-hexos-2-ulose (3-deoxy-D-fructose, **207**), which was detected in blood and urine. This conversion is likely to be biologically useful, since **207** would be less reactive, and therefore less damaging than **206**.

3-Deoxy-L-*glycero*-pentos-2-ulose is formed by oxidative degradation of L-ascorbic acid.⁴¹⁴

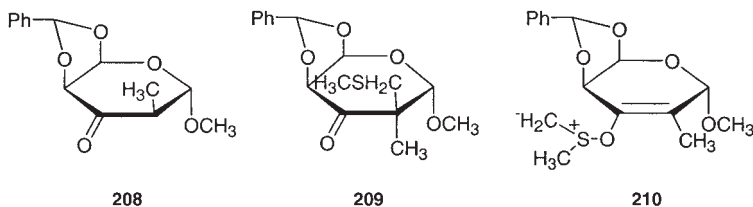
b. Preparation.—The early chemistry of the aldoses-2-uloses has been reviewed by Bayne and Fewster.⁴¹⁵ Aldoses-2-uloses may be prepared by acid hydrolysis of osazones or by transfer of the phenylhydrazine residues to simpler carbonyl compounds. In 1888, Fischer obtained D-*arabino*-hexos-2-ulose (**205**, “D-glucosone”) by treating the phenylosazone of D-glucose with hydrochloric acid; however, transhydrazonation with benzaldehyde is a more satisfactory procedure.⁴¹⁶ Purity of the osazone is important in these treatments.

A more-direct method of preparation is oxidation of aldoses, and optimal yields are afforded by the action of cupric acetate in methanol or ethanol.⁴¹⁷ This method is suitable for large-scale preparation of intermediates; however, a pure product is obtained only by chromatographic separation from the unreacted sugar byproducts. The synthesis of D-*erythro*-pentos-2-ulose and its D-*threo* isomer by oxidation of D-arabinose and D-xylose, respectively, with cupric acetate followed by anion-exchange chromatography has been reported.⁴¹⁸ The only product obtained by oxidation of D-glucose with sodium 2-anthraquinonesulfonate in alkaline

conditions is D-*arabino*-hexos-2-ulose.⁴¹⁹ Bromine oxidation (pH 7)⁴²⁰ of methyl α -D-glucopyranoside yielded mainly the 2-keto and 4-keto derivatives ($\sim 30\%$ combined); methyl α -D-galacto- and -D-manno-pyranosides, having axial hydroxyl groups in the 4 and 2 positions, respectively, give mainly the 4-keto and 2-keto derivatives. This result indicates that oxidation at a ring carbon atom having an axially disposed hydrogen atom is hindered when bulky substituents are present in *syn*-diaxial relationship. Methyl α - and β -D-xylopyranosides, upon oxidation with bromine in water in the presence of borate, give mainly the 4-glycosulides, but minor proportions of 2- and 3-ketones were also observed.⁴²¹

Lindberg and Slessor⁴²² reported the preparation of the crystalline methyl D-*erythro*-pentopyranosid-3-uloses in 50–60% yield by using a 2,4-phenylboronate protecting group during oxidation of the respective methyl D-xylopyranosides with dimethyl sulfoxide–acetic anhydride. As this protecting group is removed under very mild conditions, its introduction is useful in the preparation of those unsubstituted glycopyranosiduloses having hydroxyl groups so arranged as to complex with phenylboronic acid.

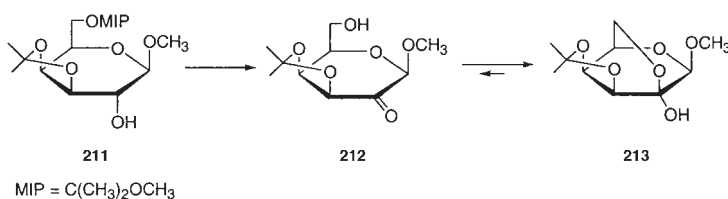
The glycosid-3-ulose derivative **208** was obtained from the corresponding D-*ido* alcohol by use of acetic anhydride–dimethyl sulfoxide for 4 h at room temperature. However, when the time was extended to 4 days, the doubly branched product **209** was obtained, by sigmatropic rearrangement of the intermediate **210**.⁴²³



An improved synthesis of 1,6-anhydro-2,3-di-*O*-benzyl- β -D-*xylo*-hexopyranos-4-ulose involves 1,6-anhydride formation from methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside and subsequent Swern oxidation.⁴²⁴

Baker and Buss⁴²⁵ used the Pfitzner–Moffatt procedure (phosphoric acid–*N,N'*-dicyclohexylcarbodiimide–dimethyl sulfoxide) for the preparation of methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy- α -D-*arabino*-hexopyranosid-2-ulose and methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy- α -D-*ribo*-hexopyranosid-3-ulose in yields of $\sim 90\%$.

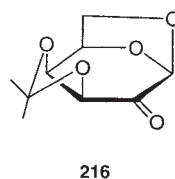
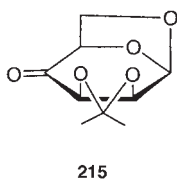
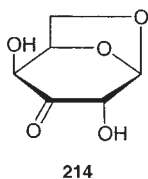
A synthesis of D-tagatose from D-galactose proceeds via the hexos-2-ulose derivative **212**, which was obtained by oxidation under Moffatt conditions from **211** and exists as the tautomeric form **213**.⁴²⁶



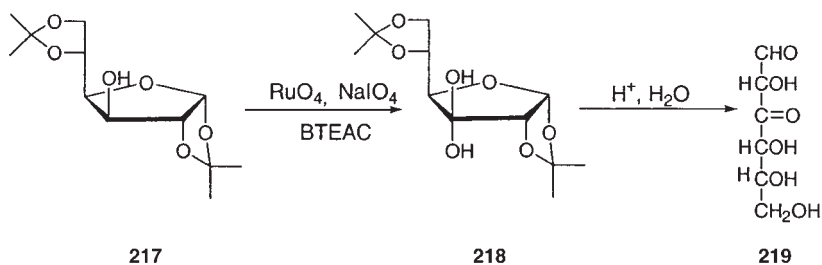
The chromium trioxide–pyridine complex affords fair yields of dicarbonyl compounds by oxidation of suitably protected precursors; 2,3:4,5-di-*O*-isopropylidene-*aldehydo*- β -D-*arabino*-hexos-2-ulose-2,6-pyranose was thus prepared in 53% yield from 2,3:4,5-di-*O*-isopropylidene- β -D-fructo-pyranose.⁴²⁷

In connection with configurational studies of the aldose moiety of the antibiotic novobiocin, Walton *et al.*⁴²⁸ prepared the exocyclic keto compound methyl 6-deoxy-2,3-*O*-isopropylidene-L-*lyxo*-hexofuranosid-5-ulose, in 73% yield, by oxidation of methyl 2,3-*O*-isopropylidene-L-rhamnofuranoside with chromic acid–pyridine. Burton *et al.*⁴²⁹ used the same oxidant to prepare the anomers of methyl 3,4-*O*-isopropylidene-D-*erythro*-pentopyranosidulose from the corresponding methyl D-*arabino*-pyranoside derivatives. Nicotinium dichromate in benzene–pyridine has been used for the low-cost, large-scale oxidation of the hydroxyl group in such compounds as 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose or 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose, in good yield.⁴³⁰ The primary alcohol is cleanly converted into the corresponding aldehydes without noticeable over-oxidation.

Heyns *et al.*⁴³¹ obtained 1,6-anhydro- β -D-*xylo*-hexopyranos-3-ulose (**214**) and six other 1,6-anhydro- β -D-hexopyranosuloses by oxygen–platinum oxidation of isomeric 1,6-anhydro- β -D-hexopyranoses.⁴³² Horton *et al.* reported the preparation of 1,6-anhydro-2,3-*O*-isopropylidene- β -D-*lyxo*-hexopyranos-4-ulose (**215**)⁴³³ from a D-*manno* precursor and of 1,6-anhydro-3,4-*O*-isopropylidene- β -D-*lyxo*-hexopyranosulose (**216**) from a D-*galacto* precursor in high yield using various oxidation conditions. Methyl anhydroglycosiduloses containing an α,β -epoxy carbonyl group have been prepared and found to be very versatile in the synthesis of deoxy, amino, and branched-chain sugars.^{434,435}



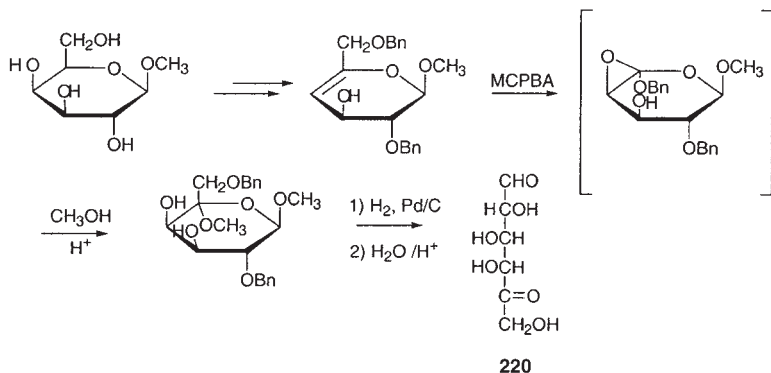
Oxidation of 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (**217**) with ruthenium tetroxide, using a phase-transfer catalyst, gave the 3-ulose derivative **218**, which by further hydrolysis afforded D-*ribo*-hexos-3-ulose **219**. Benzyltriethylammonium chloride (BTEAC) was used as the catalyst. Using the same oxidant and conveniently derivatized starting materials, α -D-*xylo*-hexofuranos-5-ulose, α -D-*ribo*-hexofuranos-5-ulose, and β -L-*arabino*-hexofuranos-5-ulose derivatives were obtained.⁴³⁶



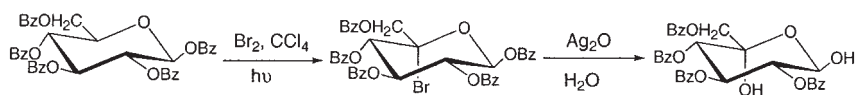
L-*arabino*-Hexos-5-ulose (**220**) can be prepared from β -D-galactopyranosides via peroxyacid oxidation of intermediate 4-deoxy- α -L-*threo*-hex-4-enopyranosides (Scheme 22).⁴³⁷

D-*xylo*-Hexos-5-ulose derivatives have been obtained from penta-*O*-benzoyl-D-glucopyranose, via photobromination at C-5 (Scheme 23).⁴³⁸

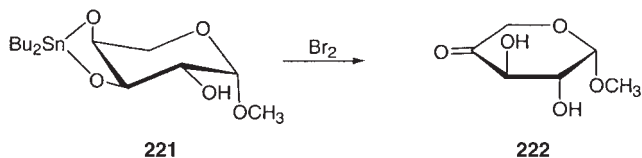
A further method of synthesizing glycosides is by brominolysis of 1,2-diol dibutylstannylene acetals. Thus, the β -L-*arabino*sides derivative **221** gave the ketone **222**, by oxidation of the axial oxy group.⁴³⁹



SCHEME 22

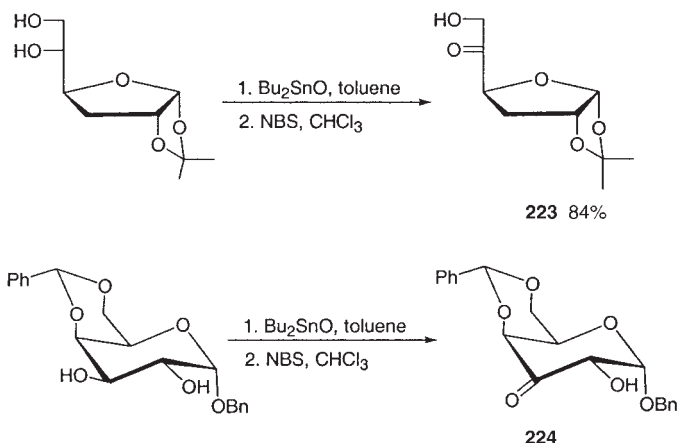


SCHEME 23

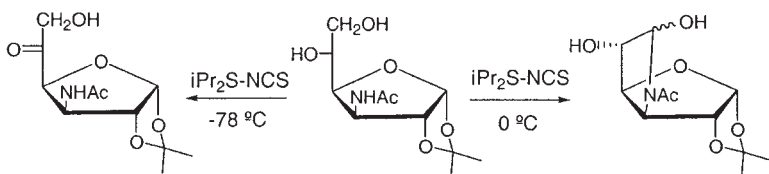


In related work, carbohydrate 1,2-diol dibutylstannylene acetals have been regioselectively oxidized by *N*-bromosuccinimide to give α -hydroxyketones. The reaction is illustrated for the preparation of 3-deoxy-1,2-*O*-isopropylidene- α -D-*erythro*-hexofuranos-5-ulose (**223**) in Scheme 24. The endocyclic diol is also regioselectively oxidized to one product (**224**) in 44% yield, although 55% of the starting compound was recovered. (Scheme 24).^{439a}

With some oxidants, interesting regioselectivity was obtained by varying the temperature conditions. Whereas the diisopropyl sulfide-*N*-chlorosuccinimide preferentially oxidizes primary hydroxyl groups at 0 °C, at -78 °C secondary groups are oxidized selectively (Scheme 25).^{439b}

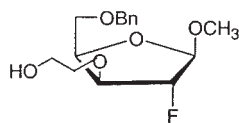
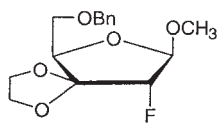


SCHEME 24

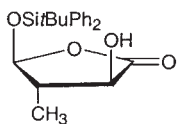
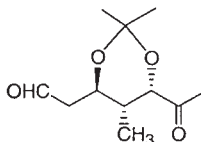


SCHEME 25

Photochemical oxidation [$\text{PhI}(\text{OAc})_2$, I_2 , $h\nu$] of 2-hydroxyethyl derivatives (such as **225**) afforded aldulose derivatives (for example **226**) as oxidation products.⁴⁴⁰

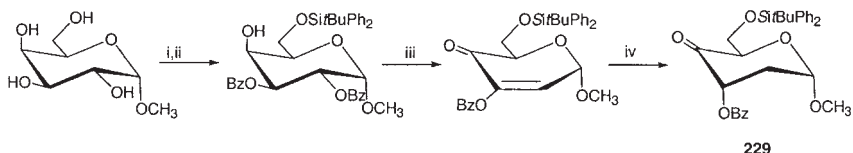
**225****226**

Lactone **227** has been converted in several steps into aldulose derivative **228**, a degradation product from the ansamycin antibiotic (+)-trienomycin A.⁴⁴¹

**227****228**

A stereospecific synthesis of methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldi-phenylsilyl)-2-deoxy-α-D-erythro-hexopyranoside-4-ulose (**229**), a precursor of thromboxane B2, has been achieved from methyl α-D-galactopyranoside according to Scheme 26.⁴⁴²

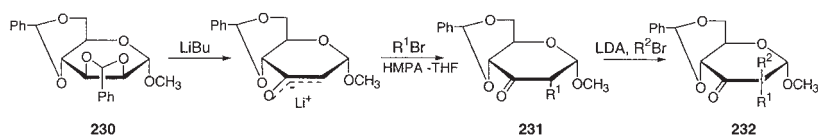
Vicinal *O*-benzylidene derivatives can be opened selectively. Reaction of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannoside (**230**) with butyllithium and



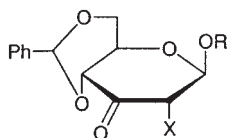
i, $t\text{BuPh}_2\text{SiCl}$; ii, BzCl , Py ; iii, Me_2SO , Ac_2O ; iv, Pd/C

SCHEME 26

alkylating agents, afforded first the 2-alkyl-3-ulosides (**231**) and then the *gem*-dialkyl compounds (**232**).⁴⁴³

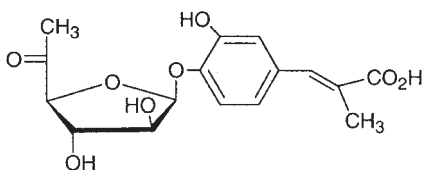


Also, opening of epoxides may afford the keto sugars. The *D-ribo* compounds **233** were obtained by treatment of the corresponding 3-nitro-*D-allo*-2,3-epoxide with nucleophiles, epimerization occurring at C-2.⁴⁴⁴



233 X = N_3 , Cl, I, H

The 6-deoxy- β -*D-arabino*-hexofuranoside-5-ulose, a constituent of the sugar-cinnamate unit **234** of the antibiotic hygromycin, and several related analogues, have been synthesized from 6-deoxy- β -*D-gluc*ofuranosides via a 2,3-epoxide and selective oxidation at C-5 with the Jones reagent.⁴⁴⁵



234

Wood-degrading fungi produce a family of pyranose oxidases (EC 1.1.3.10), enzymes catalyzing the oxidation at C-2 of several aldoses. A simple and convenient conversion of *D-glucose* into *D-arabino*-hexos-2-ulose involves the use of a pyranose-2-oxidase isolated from *Polyporus obtusus*, which was purified and immobilized on activated CH-Sepharose 4B.⁴⁴⁶

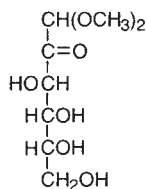
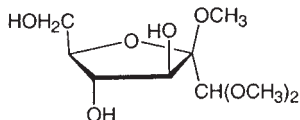
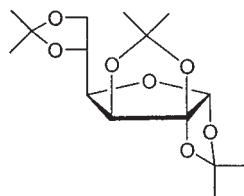
A quinone-dependent sugar oxidoreductase, purified from *Agaricus bisporus*, catalyzes C-2 and C-3 oxidation of *D-glucose* to *D-arabino*-hexos-2-ulose and preferentially to *D-ribo*-hexos-3-ulose. The two aldoketoses accumulate transiently in the reaction mixture, being converted into the same end-product, *D-erythro*-hexos-2,3-diulose. *D-Galactose* is oxidized exclusively at C-2 to produce *D-lyxo*-hexos-2-ulose.⁴⁴⁷ Fukui and Hochster⁴⁴⁸ prepared *D-ribo*-hexos-3-ulose (**219**) by enzymic oxidation and hydrolysis of sucrose.

Some microorganisms effect the oxidation of oligosaccharides to glycosid-3-uloses; this conversion has been reported for maltose, lactose, and their respective aldobionic acids. Conditions for the oxidation of sucrose by the action of *Agrobacterium tumefaciens* have been improved and optimized on a molar scale, so that "3-ketosucrose" can be produced in 40% yield.⁴⁴⁹

Use of the enzyme deoxyTDP-glucose-4,6-dehydratase on the substrate deoxyTDP-D-glucose yields the corresponding 4-keto-6-deoxy product, but this partially isomerizes to the corresponding 3-keto compound during isolation. 3-Azido-3-deoxy and 3-deoxy-dTDP-D-glucose are also substrates, affording 3-modified 6-deoxy-4-keto sugars.⁴⁵⁰ Aldos-4-ulose derivatives have been postulated as intermediates in the biosynthesis of many sugars.

c. Properties and Reactions.—The most characteristic and common properties of aldoses-2-uloses and deoxyaldoses-2-uloses, are their reduction with Fehling solution in the cold, and their ready formation of osazones. The introduction of a keto carbonyl function into an aldohexose structure generates two potential anomeric carbon atoms. Studies by ultraviolet spectroscopy have indicated that there is no appreciable proportion of the enolic form present in acidic or neutral solution. These compounds exhibit slight mutarotation, while the selective reactivity of the aldehyde group may indicate that it exists in the noncyclized form to a greater extent than does the ketone group, or that the aldehyde is more readily generated than the ketone from their respective hydrated or hemiacetal forms.

D-arabino Hexos-2-ulose (**205**) reacts with methanolic hydrogen chloride to afford D-arabino-hexos-2-ulose 1,1-dimethyl acetal (**235**) and the crystalline methyl β-D-arabino-hexos-2-ulose-2,5-furanoside 1,1-dimethyl acetal (**236**) as the main components.⁴⁵¹

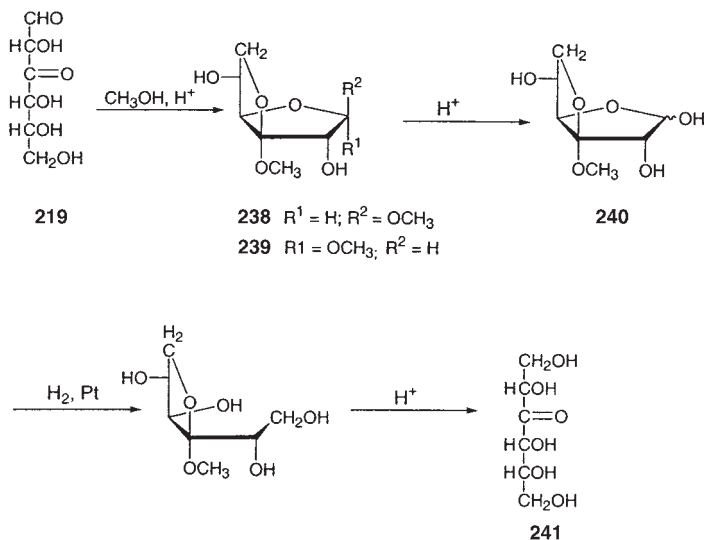
**235****236****237**

The principal synthetic application of the aldoses-2-uloses has been as intermediates in the preparation of L-ascorbic acids (see [Section II.5.a](#)). Aldoses-2-uloses can be oxidized to 2-glyculosonic acids. They are more stable

to acids than to alkalies, which catalyze enolization reactions; D-*arabino*-hexosulose (**205**) is converted into kojic acid by the action of alkali.⁴¹² Pentoses, 2-pentuloses, 3-deoxypentonic acids, and a series of aldonic acids were detected in the alkaline degradation process of compound **205**.⁴⁵² Catalytic hydrogenation of **205** over palladium on charcoal gives D-fructose with over 90% selectivity.⁴⁵³ Selective reduction of the aldehyde function in glycos-2-uloses has been performed with a recombinant human reductase, leading to 2-ketoses.⁴⁵⁴

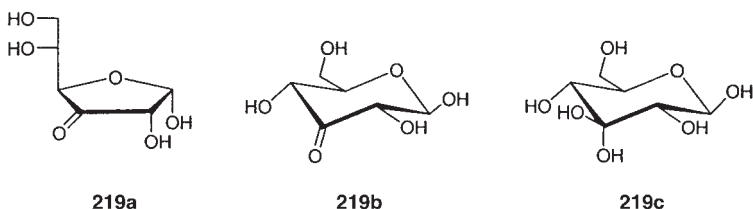
Crystalline 1,2:2,3:5,6-tri-*O*-isopropylidene-2(*R*)- α -D-*arabino*-hexofuranos-2-ulose (**237**), prepared by acetonation of **205**, is useful for purification of the aldulose, as it can be hydrolyzed, regenerating **205**.⁴⁵⁵ Aldos-2-ulose 1,1-dithioacetals have also been obtained crystalline.⁴⁵⁶

D-*ribo*-Hexos-3-ulose (**219**), treated with methanolic hydrogen chloride, afforded **238** and **239** as the main products.⁴⁵⁷ They were converted into the glycoside **240** by mild treatment with acid; this product was further converted into D-*ribo*-3-hexulose (**241**). The preparation of **241** by partial reduction of **219** was not practicable.

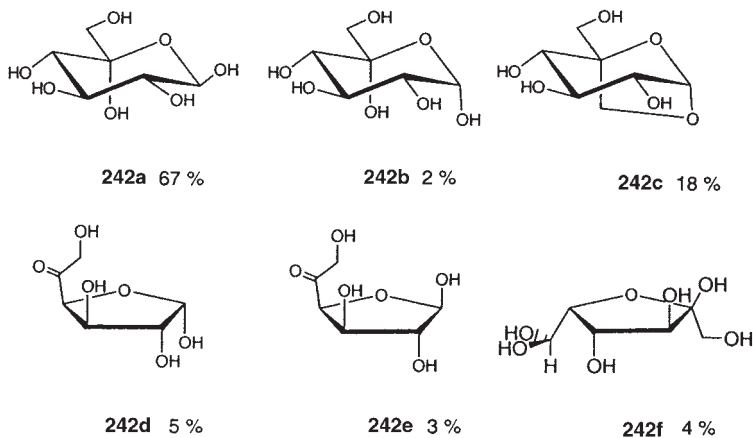


The isomeric composition of D-*ribo*-hexos-3-ulose (**219**, “3-keto-D-glucose”) in aqueous solution was also studied on the basis of NMR studies. These showed at least ten isomeric forms, with three forms predominating: α -D-*ribo*-hexofuranos-3-ulose (**219a**, 44%), β -D-*ribo*-hexopyranose-3-ulose (**219b**, 22%) and β -D-*ribo*-hexopyranos-3-ulose hydrate (**219c**, 12%), showing that the lack of crowding between an OH group at C-3 and the C-5-C-6 chain makes the resultant

furanose structure more stable in comparison to the parent glucose. ^1H NMR examination of D_2O solutions of **219** over time showed that the C-2 protons of the various isomeric forms undergo exchange with deuterium.⁴⁵⁸



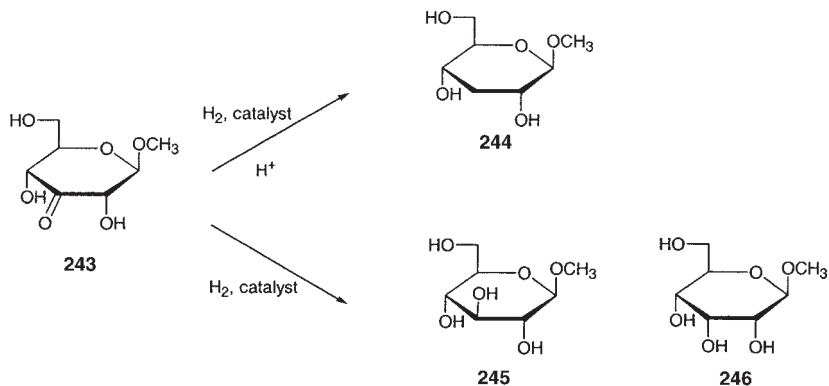
High-field ^1H and ^{13}C NMR spectra of aqueous solution of D-xylo-hexos-5-ulose (**242**) have provided evidence for the presence of at least six isomeric forms and one anhydro form. The dominant isomeric form was the β -pyranose **242a** (67%) with the next most abundant form being the anhydro structure **242c** (18%). The α - and β -1,4-furanoses (**242d,e**) and 1-aldehydrol β -5,2-furanose structure (**242f**) were also observed.⁴⁵⁹



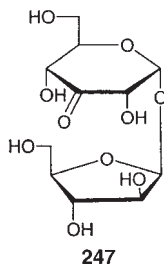
In the case of 6-deoxy- α -D-xylo-hexos-5-ulose, the NMR studies showed that the aldofuranose structures are the principal isomeric forms.⁴⁶⁰

Reduction of substituted glycosuloses has been valuable in synthetic schemes; identification of the two epimers obtained by reduction of a ketone has been used to locate the position of the ketone group. Steric factors influence various reducing reagents differently. A good example of stereoselectivity is found in the reduction of 1,2:5,6-di-O-isopropylidene- α -D-ribo-hexofuranos-3-ulose (**218**), which is reduced by

borohydride to 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose as virtually the only product of the reaction, affording an inexpensive and convenient route to the rare sugar D-allose.⁴⁶¹ Lindberg and Theander⁴⁶² found the catalytic reduction of methyl β -D-*ribo*-hexopyranosid-3-ulose (**243**) to be strongly dependent upon conditions; in acid solution they obtained primarily the 3-deoxy derivative **244**, whereas under neutral conditions they isolated a mixture of the expected epimers, namely methyl β -D-glucopyranoside (**245**) and methyl β -D-allopyranoside (**246**).



Gabriel and Ashwell⁴⁶³ prepared tritium-labeled sucrose and α -D-[3-³H]-allopyranosyl β -D-fructofuranoside by reduction of α -D-*ribo*-hexopyranosyl-3-ulose β -D-fructofuranoside ("3-ketosucrose," **247**) with tritiated borohydride.



Collins⁴⁶⁴ reported studies on *syn*- and *anti*-oximes of aldopyranosiduloses. Reduction of glycopyranosidulose oximes provides a synthetic route to amino sugars; Lindberg and Theander⁴⁶² prepared the 3-amino-3-deoxy analogues of **245** and **246** by reduction of the oxime of **243**. Taking advantage of the improvements in yields and stability brought about by protecting groups, Collins and Overend⁴⁶⁵ prepared methyl 2-amino-2-deoxy-3,4-*O*-isopropylidene- β -L-*ribo*- and -*arabino*-pyranosides by reduction

of methyl 3,4-*O*-isopropylidene- β -L-*erythro*-pentopyranosidulose oxime; reduction of the corresponding hydrazone was shown to be preparatively inferior. Brimacombe and Cook⁴⁶⁶ converted methyl 6-deoxy- α -L-*arabino*-hexopyranosidulose oxime into methyl 2-amino-2,6-dideoxy- α -L-*arabino*-hexopyranoside. The oxime route was used similarly to afford good yields of 2-amino-1,6-anhydro-2-deoxy- β -D-talopyranose and 4-amino-1,6-anhydro-4-deoxy- β -D-talopyranose.⁴⁶⁷

In separate stereoselective reactions, Rosenthal *et al.* prepared methyl 3-*C*-(2-aminoethyl)-4,6-*O*-benzylidene-2-deoxy- α -D-*ribo*-⁴⁶⁸ and D-*arabino*-hexopyranoside⁴⁶⁹ by hydrogenation of cyanomethylene or cyanomethyl groups introduced into methyl 4,6-*O*-benzylidene-2-deoxy- α -D-*erythro*-hexopyranosid-3-ulose via a Wittig reaction, or a modified aldol reaction with acetonitrile, respectively.

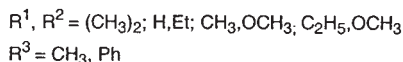
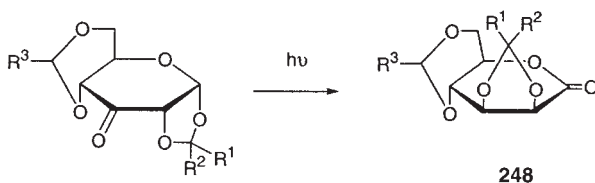
Walton *et al.*⁴²⁸ obtained methyl 2,3-*O*-isopropylidene-5-*C*-methyl-L-*lyxo*-hexofuranoside by addition of a methyl Grignard reagent to the free carbonyl group of the corresponding glycos-5-ulose.

Overend and co-workers reported numerous syntheses of sugars having methyl, hydroxymethyl, and formyl groups attached to carbon atoms of the sugar by the use of Grignard reagents,⁴²⁹ organolithium compounds,⁴⁷⁰ and diazomethane.⁴⁷¹

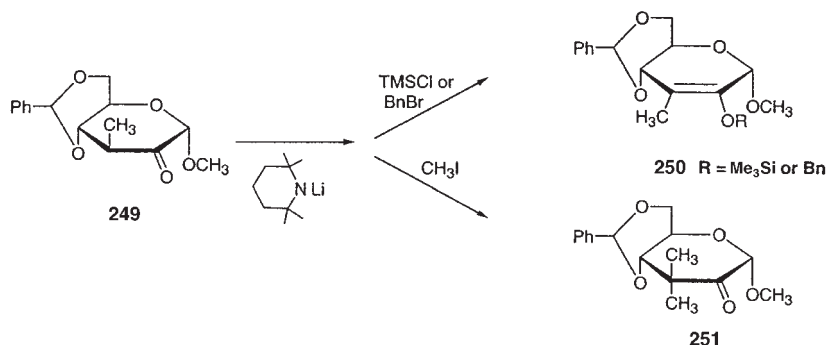
1,3-Dithian-2-yllithium is a superior nucleophile for the introduction of oxygenated, chain-branching features by addition to carbonyl⁴⁷² and epoxide groups.⁴⁷³

Dimethyl phosphite has been added to glycosulose derivatives (for example, **218**) as a means of preparing *C*-phosphono sugars.⁴⁷⁴ Methyl 2,3,6-tri-*O*-benzoyl- α -D-*ribo*-hexopyranosid-4-ulose reacts with 1,2-ethanedithiol to form the corresponding 4,4-ethylene dithioacetal.⁴⁷⁵

Pyranos-3-ulose derivatives give the D-mannono-1,5-lactones, **248**, by a photoisomerization process which may involve hydrogen transfer from C-1 to C-3, whereas furanose-3-ulose derivatives react quite differently.⁴⁷⁶



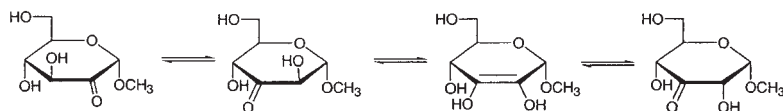
The enolate of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl- α -D-*arabino*-hexopyranosid-2-ulose (**249**) has been trapped by reaction at C=O, to give **250**, and at C-3 to give **251**.⁴⁷⁷



The isomerization of 2-oxo and 3-oxoglycosides in pyridine has been elucidated. Methyl α -D-*arabino*-hexopyranosid-2-ulose undergoes an intramolecular hydride shift, leading to α -D-*arabino*-hexopyranosid-3-ulose, which then converts to the thermodynamically more stable α -D-*ribo* isomer via an enediol intermediate, which also forms directly to a lesser extent (Scheme 27).⁴⁷⁸ The methyl α,β -D-*xylo*-hexopyranosid-4-uloses rearrange in pyridine exclusively to the methyl α,β -D-*ribo*-hexopyranosid-3-uloses via an enediol intermediate, whereas the corresponding D-*lyxo* and D-*arabino*-hexos-4-uloses come into equilibrium, again via an enediol intermediate, without leading to 3-keto compounds.⁴⁷⁹

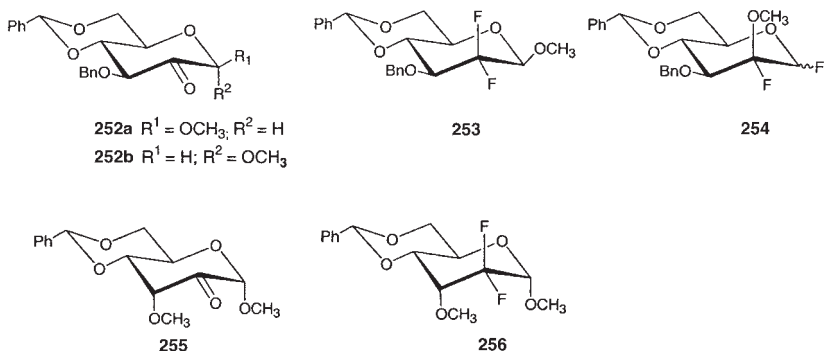
A systematic study of the reaction of different glycos-2- and 3-uloses with (diethylamino)sulfur trifluoride (DAST) was performed⁴⁸⁰ for the preparation of *gem*-difluorides. *gem*-Difluorination of glycos-2-uloses may take place effectively, but only if the neighboring groups have the same configuration, as shown in the following examples.

Reaction of methyl 3-*O*-benzyl-4,6-*O*-benzylidene- β -D-*arabino*-hexopyranosid-2-ulose (**252a**) with DAST in dichloromethane at room temperature affords the difluorinated compound **253** in 80% yield. However, the α anomer **252b** did not react at room temperature, and by heating in benzene the migration product **254** was obtained as a mixture of anomers.

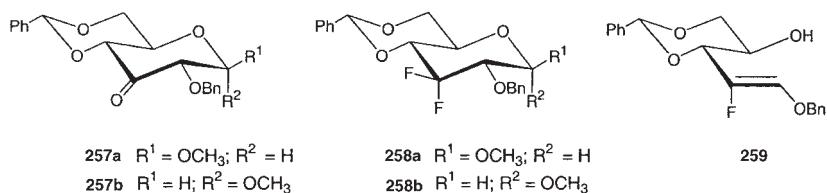


SCHEME 27

Compound **255** gave the difluoro compound **256** in 38% yield when refluxed with DAST in dichloromethane.⁴⁸⁰



3-Glycosuloses are *gem*-difluorinated with DAST in only moderate yields because of a competitive fragmentation reaction. When the 3-uloses **257a** and **257b** were treated with DAST, compounds **258a** and **258b** were obtained as the main products in 40 and 48% yields, respectively. The ring-opened compound **259** was isolated as a byproduct in both cases.⁴⁸⁰



Other methods of preparation and reactions of glycosuloses are described in Ref. 336.

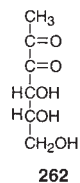
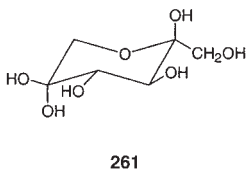
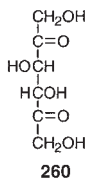
3. Glycodiuloses

Members of this group have been obtained by synthesis or by microbial oxidation; a few examples have been isolated as intermediates in the degradation of carbohydrates.

Diuloses and alduloses are the main products when aqueous solutions of sugars are gamma-irradiated in the presence of oxygen.⁴⁸¹

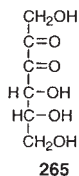
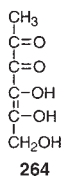
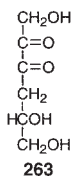
a. Preparations.—*D-threo*-2,5-Hexodiulose (“5-keto-*D*-fructose,” **260**) can be obtained by microbial oxidation of *D*-fructose with many species of *Acetobacter* and *Gluconobacter*.⁴⁸² X-Ray crystallographic analysis of **260** shows that it crystallizes as an unsymmetrical dimer.⁴⁸³ Compound **260** is

produced by oxidation of D-fructose at C-5 through the action of D-fructose 5-dehydrogenase.⁴⁸⁴



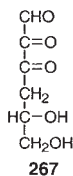
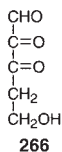
The structure of **260** in solution has been shown by ¹³C NMR spectroscopy to be the pyranose form **261** with the 5-keto group hydrated.⁴⁸⁵

Ishizu *et al.*⁴⁸⁶ synthesized L-deoxy-D-erythro-hexo-2,3-diulose (**262**) as a possible intermediate in the production of saccharinic and other acids. A related compound, 1,5-anhydro-6-deoxy-L-erythro-2,3-hexodiulose, was obtained by pyrolysis of a cardiac glycoside of *Calotropis procera* by Crout *et al.*⁴⁸⁷ 4-Deoxy-D-glycero-2,3-hexodiulose (**263**) was isolated by Machell and Richards⁴⁸⁸ and by Whistler and BeMiller⁴⁸⁹ as an intermediate in the formation of “D-glucoisosaccharinic” acids during the degradation of 4-O-substituted D-glucose derivatives. Harris and Feather⁴⁹⁰ discussed the possible role of **262** and 1,5-dideoxy-hex-4-eno-2,3-diulose (**264**) as intermediates in the acid-catalyzed degradation of D-glucose and D-fructose.



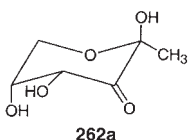
Crude enzyme extracts from the white-rot fungus *Oudemansiella mucida* oxidize D-glucose to D-erythro-hexos-2,3-diulose (**265**) via D-arabino-hexos-2-ulose. Compound **265** was identified by NMR and mass spectroscopy of the *N,N*-diphenylhydrazone derivatives.⁴⁹¹

An immobilized enzyme preparation of pyranose-2-oxidase catalase and 2-ulose dehydratase effects the conversion of D-xylose and 6-deoxy-D-glucose into 5-hydroxy-2,3-dioxopentanal (**266**) and D-glycero-5-hydroxy-2,3-dioxohexanal (**267**), respectively.⁴⁹²



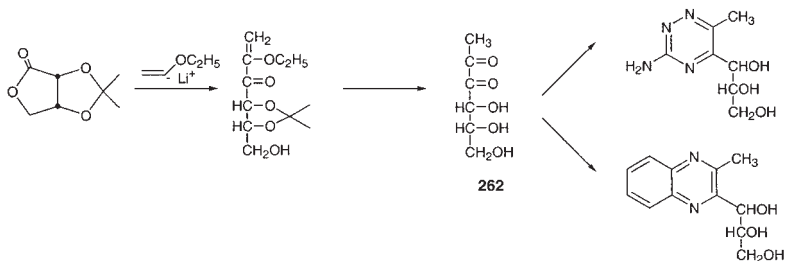
α -Dicarbonyl compounds constitute a major group of reactive intermediates in the reaction of reducing sugars with amines. This reaction takes place during food processing and is called the Maillard browning reaction. It is responsible for desirable attributes of flavor and color, but also has negative consequences, such as the loss of essential amino acids and generation of mutagenic compounds. In addition, the Maillard reaction occurs *in vivo* and is thought to have considerable impact on diabetes and aging.⁴⁹³ 1-Deoxy-D-*erythro*-hexos-2,3-diulose (**262**) is the more reactive Maillard intermediate.⁴⁹⁴ A stereoselective synthesis of **262** starts from 2,3-*O*-isopropylidene-D-erythrone. Reaction with ethoxyvinyl lithium as an acyl equivalent leads to formation of the six-carbon backbone (Scheme 28). The diulose **262** was characterized as the triazine derivative by reaction with aminoguanidine. Compound **262** also gives a stable quinoxaline derivative by reaction with *o*-phenylenediamine.

The ^1H and ^{13}C NMR data for **262** showed that the major isomer in solution is the 2,6-pyranose in the $^2\text{C}_5$ -chair conformation, **262a**.

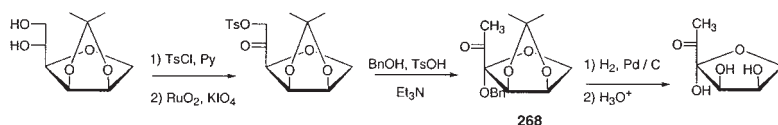


The 1-deoxy-D-*erythro*-2,3-hexodiulose derivative **268** has been synthesized by ruthenium oxide–periodate-promoted oxidation of a D-glucufuranose derivative, followed by an unusual rearrangement (Scheme 29).⁴⁹⁵

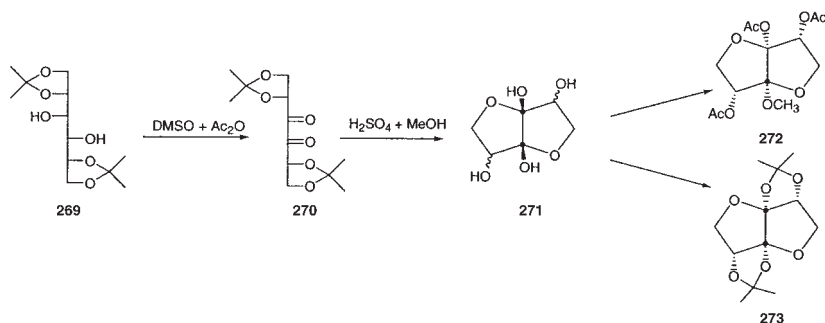
Oxidation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**269**) with dimethyl sulfoxide–acetic anhydride gave the 3,4-diulose derivative **270**, which on hydrolysis led to crystalline **271**. Some derivatives, such as **272** and **273** have been prepared.⁴⁹⁶



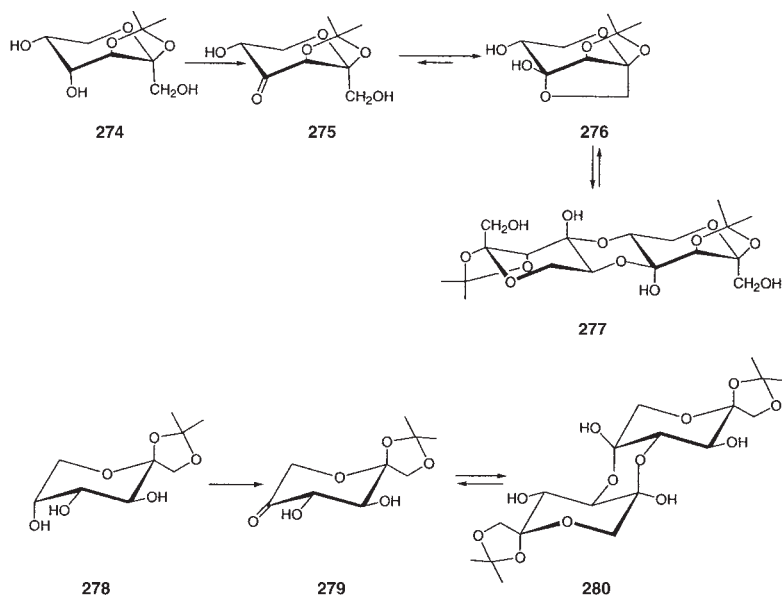
SCHEME 28



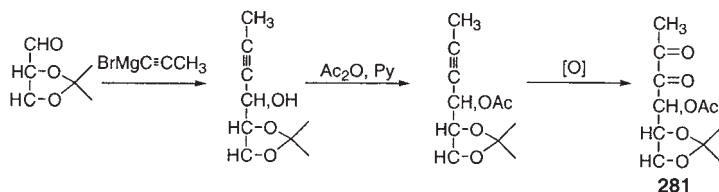
SCHEME 29



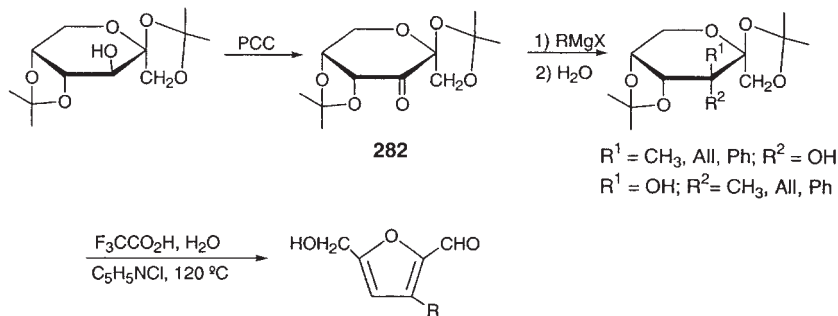
Stannylation of 2,3-*O*-isopropylidene- β -D-fructopyranose (**274**) with dibutyltin oxide followed by brominolysis afforded 2,3-*O*-isopropylidene β -D-*threo*-hexo-2,4-diulopyranose (**275**). Compound **275** equilibrates to a mixture of the hemiacetal **276** and the symmetrical dimer **277**. 1,2-*O*-Isopropylidene- β -D-fructopyranose (**278**) afforded 1,2-*O*-isopropylidene- β -D-*threo*-hexo-2,5-diulopyranose (**279**), which dimerizes to **280**.⁴⁹⁷



The epimeric diketones **281** have been synthesized by condensing 2,3-*O*-isopropylidene-D-glyceraldehyde with propyne via a Grignard reaction, followed by oxidation of the *O*-acetylated epimers to the diketones using a ruthenium catalyst and iodosylbenzene as the oxidant.⁴⁹⁸

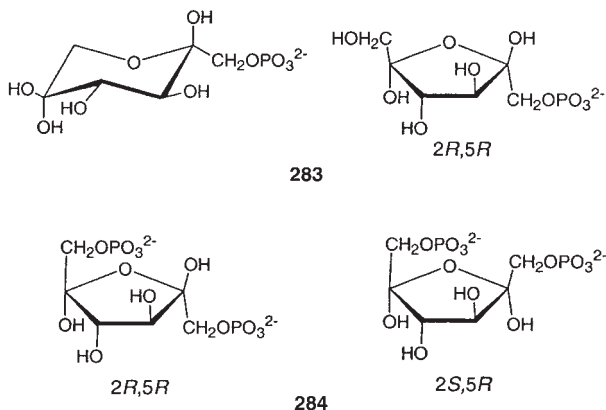


b. Reactions.—Addition of Grignard reagents to hexadiulose **282**, obtained by oxidation of 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose, gave the corresponding C-3 substituted hexuloses. These can be converted into 3-substituted 5-hydroxymethyl-2-furancarboxaldehydes by heating with pyridinium chloride (Scheme 30).⁴⁹⁹



SCHEME 30

The mono- (**283**) and bis-phosphate (**284**) derivatives of D-*threo*-2,5-hexadiulose ("5-keto-D-fructose," **260**) were synthesized enzymically and purified by anion-exchange chromatography. The proportions, ring size, and anomeric configuration were determined by ³¹P and ¹³C NMR spectroscopy. Compound **283** was found to exist preponderantly (80%) in the β -pyranose form, with the remainder being present in the 2*R*,5*R*-furanose form. Compound **284** assumes two different furanose forms in solution, one (~80%) being the 2*R*,5*R*-furanose and the other the 2*R*,5*S*-furanose.⁵⁰⁰



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OXIDATIVE REACTIONS AND DEGRADATIONS OF SUGARS AND POLYSACCHARIDES*

BY OSCAR VARELA

CIHIDECAR (CONICET), Departamento de Química Orgánica, Facultad de Ciencias Exactas
y Naturales, Pabellón 2, Ciudad Universitaria, 1428 Buenos Aires, Argentina

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*This article updates the treatment of this subject by J. W. Green¹ in the 1980 second edition of "The Carbohydrates, Chemistry and Biochemistry," edited by W. Pigman and D. Horton, and follows the same general layout of topics. While the emphasis is on newer material, the fundamental concepts of sustained importance are included. Where appropriate, the reader is directed to Green's original article for additional details on individual topics.

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I. INTRODUCTION

The oxidation of carbohydrates is an important tool for obtaining compounds having interesting chemical and physical properties. Such oxidation products constitute useful intermediates for the synthesis of more complex molecules, and they also display, in many cases, varied biological activities. The oxidation at the anomeric center and of the hydroxymethyl group of monosaccharides is well documented. Selective oxidation of primary hydroxyl groups or the glycolic oxidation of polysaccharides yields polycarboxylates having thickening, gel-forming, and metal-sequestering properties.

Oxidation in organic chemistry refers to the elimination of hydrogen atoms from a substrate, or to the replacement of a hydrogen atom bonded to carbon by a more electronegative element, oxygen in particular. As a more general concept, the oxidation of an organic compound involves the transfer of electrons from the substrate to the oxidant, a process that is usually accompanied by the breaking of carbon–hydrogen or carbon–carbon bonds. Such a reaction, which can formally be regarded as occurring between a nucleophile (the substrate) and an electrophile (the oxidant), is greatly affected by factors that alter the nucleophilicity or electrophilicity of the respective reactants; steric effects are often also important. A brief discussion of these factors is given first, and more-specific examples, together with mechanistic aspects and synthetic applications of these reactions, are presented in [Sections II–XIII](#). These subjects have been previously reviewed,^{1–4} and they are also discussed in the preceding article on oxidation products.

1. Heterolytic Oxidations

The two-electron oxidation of a secondary alcohol group can be regarded as an elimination of two hydrogen atoms and the formation of a double bond between the carbon atom and the oxygen atom. [Equation \(1\)](#) illustrates breakage of a C–H bond with elimination of a nascent hydride ion: this anion is a poor leaving group, but its removal is aided by the

oxidant, which captures the pair of electrons and converts the hydride ion into a proton.



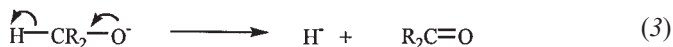
The O–H bond dissociates with the liberation of a proton; this bond-breaking is readily accomplished with the aid of a base, usually the solvent. Thus, the breaking of the C–H bond is generally the slow (rate-determining) step of the reaction.

In principle, the flow of electrons shown in Eq. (1) can also occur in the reverse direction, with elimination of the hydrogen atom from the hydroxyl group as a hydride ion. Evidence for such a mechanism has been given.^{5,6}

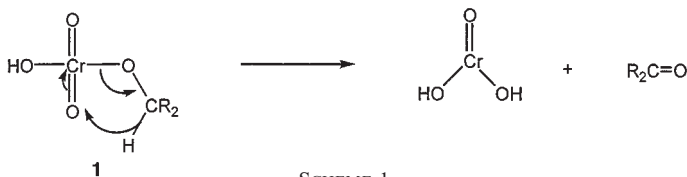
The oxidant may aid the elimination in a concerted or E₂ type of mechanism, as illustrated in Eq. (1); for such examples, the oxidant is not bonded to the substrate, except possibly in the transition state. Other oxidants, for example chromic acid, have been shown to form intermediate esters such as **1** (although other mechanisms have been proposed⁷), which subsequently decompose by a related, bimolecular elimination [Eq. (2)]; here the leaving group is the reduced form of the oxidant, and the C–H bond must necessarily break with the liberation of a proton. As in Eq. (1), the capture of electrons by the oxidant is the driving force of the reaction, so that the breaking of the C–H bond occurs simultaneously in the rate-determining step (Scheme 1).



Variations of the foregoing two reactions are often encountered. Alkoxide ions, being relatively strong bases, can be considered to be reducing agents,⁸ as they are able to eliminate hydride ions [Eq. (3)].



Glycols are more acidic than monohydric alcohols⁹ and the C-1 group on an aldopyranoid compound is even more acidic, owing to the inductive effect of the ring-oxygen atom; therefore, sugars are more readily oxidized than ordinary alcohols. For the free sugars, however, oxidations at higher pH are accompanied by competing processes of epimerization and of degradation to saccharinic acids; this factor is discussed in Section II (see also preceding chapter).



SCHEME 1

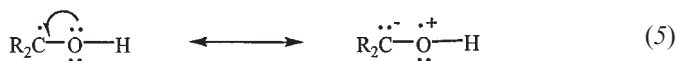
2. Steric Effects

The β anomers of sugars are generally oxidized more rapidly than the α anomers (see later), a similar pattern is seen in the faster oxidation of β -glycosides. The different rates of oxidation of β -D-glucopyranosides and their α -D anomers have been attributed to the equatorial orientation of the anomeric hydroxyl group in the 4C_1 conformation of the former. Other compounds have shown a similar behavior.¹⁰ Thus, the relative rate of oxidation of *cis*-2-*tert*-butylcyclohexanol (HO-axial) with respect to the *trans* isomer (HO-equatorial) is approximately 5:1.

The oxidation of a secondary hydroxyl group of glycopyranosides involves the conversion of a tetrahedral carbon atom into a trigonal one, and there may be some resistance to the introduction of this constraint into the ring. Baker and Haines¹¹ pointed out the greater ease of oxidation of acyclic than of cyclic sugar derivatives; however, more-powerful oxidants may give good yields of glycosiduloses.¹²

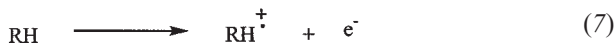
3. Homolytic and Electron-Transfer Oxidations

As termolecular reactions are very rare, the transfer of two electrons must necessarily occur in two successive steps in reactions of one-electron oxidants. The first step is the formation of a radical [Eq. (4)]; the oxidant facilitates removal of the hydrogen atom, converting it into a proton. Resonance stabilization [Eq. (5)] of the resulting radical is regarded as more important than inductive effects. For stabilization of the radical, an adjacent atom (such as oxygen) having unshared pairs of electrons is necessary; therefore, initial attack generally occurs at a C–H bond adjacent to an oxygen atom, rather than at an O–H bond adjacent to a saturated carbon atom, which is incapable of participating in resonance stabilization. Thus, alkoxy radicals are electrophiles and they preferentially attack C–H bonds with high HOMO energies, for example the α -C–H bond of ethers and alcohols.¹³ This is illustrated by the favored catalytic oxidation of glycosides having axially attached hydroxyl groups, because the attack is initially upon the sterically more available equatorial C–H bonds.

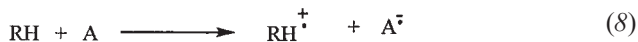


The final step is homolysis of the O–H bond in the radical to afford the carbonyl product plus a second hydrogen radical, which is converted by the oxidant into a proton [Eq. (6)]. Equation (4) is the slow or rate-determining step; removal of the second hydrogen atom is rapid.

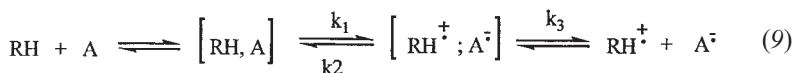
Electron-transfer oxidation of organic compounds involves multiple steps with transient radicals as key reactive intermediates.¹⁴ The electron-transfer oxidation of a neutral, diamagnetic organic donor (RH), having an even number of electrons, produces a radical cation, as shown in Eq. (7).



The energetic basis for the electron-transfer oxidation includes the thermodynamic potential of oxidation (E_{ox}°) for the electron transfer from RH in Eq. (7). Such an electron detachment is commonly effected at an electrode, by an oxidant, or with light. The oxidation is driven electrochemically by the anodic electrode potential, which matches the E_{ox}° value. Likewise, the driving force in the chemical oxidation of RH is provided by the redox potential (E_{red}°) of the electron acceptor or oxidant (A) according to Eq. (8).



Electron-transfer oxidation can be considered to consist of a series of equilibria as shown in Eq. (9), with formation of an electron donor–acceptor precursor complex, which leads to the contact ion-pair constrained by the solvent cage. Intermolecular reactions of $\text{RH}^{\cdot+}$, which lead to oxidation products, take place after escaping from the cage.¹⁴



Photochemical electron-transfer can be effected by irradiation of the charge-transfer absorption band of the electron donor–acceptor complex.¹⁵ Alternatively, photochemical electron-transfer may proceed by actinic activation of RH followed by quenching with A, or by the reverse sequence involving activation of A and quenching with RH.

4. Electrophilic Nature of the Oxidant

Although the effect of increasing pH, already mentioned, is to increase the susceptibility of the substrate to oxidation, this increase generally decreases the effectiveness of the electrophilic oxidant at the same time. Permanganic acid is more effective than the permanganate anion as an oxidant.¹⁶ Wet

combustions, the complete oxidation of organic compounds under strongly acidic conditions to carbon dioxide and water, may occur because of the extreme electrophilicity of the protonated oxidant. Thus, the two extremes of pH, extremely strong acid and extremely strong alkali, favor complete oxidation.

The effectiveness of an oxidant as an electrophile is roughly proportional to its "acidity" or lack of basicity. Phenylhydrazine, a weak base, is a very weak oxidant; however, substitution of nitro groups on the aromatic ring decreases the basicity and increases the potency of the hydrazine as an oxidant.

Another factor is the leaving-group ability, which is of importance in oxidations by peroxides and halogens. Such oxidants, reacting with a substrate S, tend to form an HO^+ or X^+ cation in the transition state and lose the rest of the molecule as an anion [Eq. (10)]; the more effective as a leaving group is X^- , the better is HOX or X_2 as an oxidant. Hydrogen peroxide, which must displace a strongly basic OH^- group, is a poor oxidant, whereas peroxyacetic acid, which reacts to displace the resonance-delocalized acetate anion, is a good oxidant. The nucleophilic nature of the sulfinyl oxygen of sulfoxides, and the good leaving-group properties of dimethyl sulfide, have been used effectively for the oxidation of primary and secondary hydroxyl groups (see Section IX).



Oxidants often tend to disproportionate by interaction of the acidic or undissociated oxidant with the anion of the same oxidant;¹ this is a nucleophilic displacement, by the OX^- anion, of X^- from the oxygen atom of the electrophilic HOX [Eq. (11)]. Two points should be emphasized here. First, the maximum decomposition occurs when HOX and OX^- are in equal concentrations, that is, when the pH of the reaction is equal to the pK_a of the oxidant [Eq. (12)]. Second, since this is a displacement, the reaction goes more readily when the group X^- is easily displaced; thus formation of iodate from hypoiodite is more extensive than chlorate formation from hypochlorite.



$$\text{K}_a = [\text{H}^+] \frac{[\text{OX}^-]}{[\text{HOX}]} = [\text{H}^+]; \quad \text{pK}_a = \text{pH} \quad (12)$$

Although the examples illustrated in Eqs. (1-6) and (10) are given as secondary alcoholic groups, primary alcoholic groups can be treated similarly. Oxidation of the anomeric carbon atom in reducing sugars

(H-CR₂-OH grouping) proceeds much as for a secondary hydroxyl group. Oxidation of an H-CR₂-OMe grouping (e.g., in an aldoside) is, however, quite different, because the readily displaceable hydrogen atom has been replaced by a methyl group, which is eliminated with great difficulty. Thus, oxidative attack on aldoses often takes place on available secondary or primary alcoholic groups, rather than on C-1.

II. HALOGEN OXIDATIONS

Bromine (hypobromite) and hypoiodite oxidations are particularly useful for the preparation of aldonic acids from aldoses and of aldaric acids from glycuronic acids. Primary alcohol groups also undergo oxidation by these reagents, although this conversion is of less value; glycosides can thus be converted into glycosiduronic acids, and alditols into aldoses and aldonic acids.

Secondary alcoholic groups are slowly oxidized to ketone groups, and 2-glyculosonic and 5-glyculosonic acids are formed in this way. More-extended oxidation results in the cleavage of carbon-carbon bonds and in the production of chain-shortened acids.

The halogens and their oxyacids, particularly chlorine and hypochlorous acid, are widely used as oxidizing and bleaching agents. These properties are related to the variations of redox potentials.¹⁷

1. Halogens and Hypohalites

The oxidation with halogens and hypohalites is a complicated reaction, as it depends strongly on the conditions of temperature, acidity, and concentration of the reacting species. The halogens show considerable differences in the positions of the various equilibria and the speed with which the equilibria are attained (see Table I). In acidic solution, the equilibrium between free halogen and hypohalous acid [Eq. (13)] lies far to the left, and the concentration of hypohalous acid is very low. When alkali is added to the system, the concentration of hypohalite ion increases, according to Eq. (14).



Hence, the concentrations of free halogen, halic acid, and hypohalite vary greatly with the acidity. For example, at pH 1, the total chlorine present

TABLE I
Selected Properties of Halogens, Halides, and Hypohalous Acids

Halogen	Cl	Br	I	References
Solubility of X ₂ in water (mol/L) at 25 °C	0.092	0.2141	0.013	18
<i>K</i> for X ₂ + H ₂ O ⇌ HOX + HX	4.5 × 10 ⁻⁴	2.4 × 10 ⁻⁸	3.6 × 10 ⁻¹³	1
<i>k</i> , in sec ⁻¹ , for X ₂ + H ₂ O → HOX + HX	11	110	3	1
p <i>K</i> _a , for HOX ⇌ H ⁺ + OX ⁻	7.40	8.55	10.5	1
<i>E</i> ₀ , in volts, for 2X ⁻ ⇌ X ₂ + 2e ⁻	-1.356	-1.065	-0.535	18
Leaving-group tendency, <i>k</i> _x / <i>k</i> _{Br} (average)	0.02	1.0	3.0	1

exists as (82%) free chlorine and as (18%) hypochlorous acid; whereas at pH 8, 21% exists as hypochlorous acid and 79% as hypochlorite.

Hypohalites are converted into halates according to the following equations:



As mentioned in Section I, disproportionation occurs most rapidly at a pH corresponding to the p*K*_a value [Eq. (12)]. The velocity of formation of halate increases greatly in the order ClO₃⁻ < BrO₃⁻ < IO₃⁻; this order correlates directly with the leaving-group tendencies of the respective halide ion (see Table I).

a. Oxidation in Acidic and Neutral Solutions.—In acidic solution, the active oxidant is normally the free halogen molecule (for chlorine or bromine systems), and the hypohalous acid is less effective; this may derive from the relative stabilities of the anionic products of the oxidation, as the halogen, X₂, has two potentially good leaving-groups [see Eq. (10)], whereas the acid HOX has only one such group. The order of effectiveness as an oxidant, however, is in the order Br₂ > Cl₂ > I₂, the last being very ineffective. This order corresponds neither to the oxidation potentials (Table I) nor to the order of leaving groups; it does, however, correspond to the higher solubility and the rate of hydrolysis of the free halogen by water (*k* in Table I).

As already mentioned, the relative proportions of free halogen and hypohalous acid vary with the acidity of the solution and the nature of the halogen; however, unless a buffer or neutralizing compound is present, the

solution becomes strongly acidic as a result of the formation of hydrohalic acid during the oxidation of an organic substrate [see Eqs. (17) and (18)].



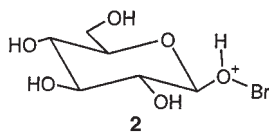
As described in Ref. 1 (pp. 1108, 1109), the first reports on the use of halogens for the oxidation of sugars to aldonic acids appeared by the end of the 19th century. The accumulation of hydrogen bromide during oxidations by bromine profoundly decreases the rate of further oxidation. This effect results from the increase in acidity and also may be due to complexation of free bromine as Br_3^- , which is ineffective as an oxidant. To minimize this inhibiting influence, the reaction may be conducted in the presence of a solid buffer, such as barium carbonate or calcium benzoate. In general, the presence of a buffer increases the yield of aldonic acid, and, in addition, it precludes the hydrolysis of disaccharides. Yields of 96% of D-gluconic acid and of 90% of D-xylonic acid (as salts) have been obtained from oxidation of the respective aldoses in buffered solutions. When the oxidation period is extended, particularly under unbuffered conditions, keto acids may be formed in low yields. Under more-drastic conditions, carbon-carbon bonds are cleaved, to yield chain-shortened acids.

A variation of the bromine oxidation process is the electrolytic oxidation of sugars in the presence of a bromide, and a solid buffer, such as calcium carbonate. The electrolytic reactions of sugars have been reviewed.¹⁹ Presumably, the reaction occurs because of the formation of free bromine at the anode; the bromine oxidizes the aldose to the aldonic acid and is itself reduced to bromide. Yields are almost theoretical in many cases. If the electrolytic method is not well controlled, aldaric acids and 2- and 5-glyculosonic acids may be produced. Studies on the anodic oxidation of glucose using bromide and hypobromite ions as redox mediator have been conducted.²⁰ Such studies revealed that the rate of oxidation is independent of the glucose concentration but it is significantly affected by the interfacial mass transfer and the initial concentration of mediator. The electrolytic oxidation of lactose to yield calcium lactobionate has been optimized.²¹ The process uses rotating graphite anodes, stationary graphite cathodes, and NaBr solution to electrogenerate Br^-/BrO^- . The continuous electrochemical oxidation of D-glucose yielded 94% conversion into sodium gluconate using a filtering anode made from carbon fibers and an optimum concentration of NaBr, buffered at pH 9, as electrolyte.²² Other electrochemical oxidations of carbohydrates are described in the preceding chapter.

Ketoses are generally resistant to the action of bromine,¹ and bromine oxidation is sometimes used to remove aldoses from such mixtures as invert sugar. By extending the period of oxidation and employing high temperatures, degradation products are obtained from 2-ketoses. Under milder conditions the oxidation of ketoses leads to 5-hexulosonic acids. Calcium D-*arabino*-2-hexulose-5-phosphate yielded 65% of calcium D-arabinonate by electrolytic oxidation with bromine.¹⁹ For bromine oxidations of polyols, more-drastring conditions are needed than for aldoses. Cyclitols are also oxidized by the action of bromine in a buffered solution.²³

Methyl α - and β -pyranosides of galactose, glucose, and mannose have been oxidized by bromine at neutral pH. Oxidation of secondary hydroxyl groups afforded 2-, 3-, or 4-uloses. A low degree of oxidation of the primary alcohols was also reported, although the initial products are rapidly converted into uronic acids.²⁴ Similarly, nonreducing disaccharides, α and β cyclodextrins (cyclomaltohexa- and heptaoses) and their derivatives have been oxidized by aqueous bromine solution at pH 7. Both ketone and carboxylic acid-containing materials are among the products of the oxidation.²⁵ A pH dependence for the reaction of bromine with cyclodextrin shows that the maximum rate of bromine loss roughly coincides with the maximum concentration of HOBr, indicating that this is the reactive species in these oxidations. A mechanism was suggested involving the attack of HOBr to one of the secondary HO groups of cyclodextrin, with Br⁻ leaving to yield an intermediate dehydroxy hydroperoxy cyclodextrin that subsequently decomposes to a keto-cyclodextrin. An alternative pathway prevails when the reaction is carried out under alkaline conditions, where carboxylic acids are the main products.

b. Mechanism of Bromine Oxidation of Aldoses.—Free bromine is the active oxidant of aldoses when they are treated with bromine in the presence of barium carbonate and bromides (pH about 5.4). Similarly, molecular chlorine was found to be the active oxidant in the oxidation of D-glucose by buffered chlorine–water at pH 2.2 and 3.¹ Interestingly, it is the cyclic forms of an aldose, and not the acyclic free aldehyde form, which are oxidized directly under these conditions. Pyranoses afford 1,5-lactones, and furanoses, 1,4-lactones, in high yield. The anomERICALLY equilibrated solutions are oxidized at rates intermediate between those for the individual anomers, and the oxidation curve is composed of a rapid phase followed by a slow one. A detailed discussion on the kinetics of this type of oxidation has been given in Ref. 1, pp. 1110–1112. It is important to point out that the rate of bromine oxidation observed for α -D anomers suggests a dependence of the rates of mutarotation into the β -D anomers, and that the true rates of oxidation of the α -D anomers are much lower. Thus, the rate-determining



SCHEME 2

step in the oxidation of the α -D anomers is anomerization to generate the faster-reacting β -D anomer. For D-glucose, the true rate of oxidation of the α anomer was found to be about 1/250th that of the β anomer. It has been suggested that the higher rate of oxidation of β -D-glucopyranose is due to the equatorial orientation of the hydroxyl group on C-1; this group is less hindered for reaction with the bromine molecule, to give a cationic intermediate (**2**). Also its structure is stereoelectronically favored, as the positive charge is located on the anomeric substituent, which has the β configuration (reverse anomeric effect²⁶). This intermediate undergoes conversion into D-glucono-1,5-lactone, via a hypobromous ester (see Ref. 1, pp. 1111–1114). However, Isbell²⁷ proposed an alternative explanation based on the difference in free energy between the respective ground and (presumed) transition states of the two anomeric anions derived from D-glucopyranose. The transition states are assumed to be similar in structure for both anomers; however, the transition state for the β -D anomer suffers less destabilization by nonbonded interactions (Scheme 2).

The increase in the rate of oxidation of aldoses with increase in pH from 1.25 to 4.5 was attributed to the progressively enhanced extent of participation by the anion of the aldose, which undergoes oxidation faster than the neutral aldose;²⁸ however, this implies a difference in reactivity of about 10^{11} and such an extreme difference in rate could not be explained by a difference in acidity only. Furthermore, relative rates of oxidation by bromine decrease in the order: β -L-arabinose > β -D-galactose > β -D-glucose > β -D-mannose, which precisely reverses the order of the extents of dissociation of these aldoses. Whereas the foregoing reactions of aldoses involve a free hydroxyl group at C-1, alkyl β -D-glucosides are also more readily oxidized by acidic chlorine, and also by alkaline hypochlorite, than the α -D-glucosides. As no hypohalite ester can be formed directly at the anomeric carbon atom, the relationship of oxidizability of the sugar to the acidity of the anion is not straightforward.

c. Oxidation of Aldopyranosides with Acidic Chlorine Systems.—

Oxidation of methyl D-glucopyranosides with saturated chlorine–water (unbuffered, pH~1 initially) affords D-gluconic acid as main product, which is oxidized further to D-xyl/o-2-hexulosonic acid and D-glucaric acid.

In Ref. 1 (pp. 1114–1115) the effect of the axial or equatorial orientation of the aglycon in the rate of oxidation of a number of β -D-glycopyranosides is described. When the aglycon adopts an equatorial orientation [a β anomer in the ${}^4C_1(D)$ conformation] the oxidation takes place at a higher rate (two to ten times) than for the α anomer. In the case of methyl L-arabinopyranosides, the α -L anomer, which, in the ${}^1C_4(L)$ conformation has an equatorially attached group at C-1, is oxidized more rapidly.

Chlorine oxidation of methyl β -D-glucopyranoside to D-gluconic acid is very slow (50% conversion after 14 days at room temperature). The D-glucoside is, apparently, oxidized directly to D-gluconic acid, without initial hydrolysis of the glycosidic linkage. The oxidation of methyl β -D-glucopyranoside was conducted at several pH values; the major products formed at pH 4 were D-gluconic, D-erythronic, and glyoxylic acids; minor products were D-glucose, D-arabinose, and hexopyranosiduloses. Hypochlorous acid was considered to be the oxidant, based on the observations that the concentration of this species is maximum at pH 4 and that the yield of neutral products from the oxidation was also at a maximum at this pH value.¹

d. Oxidation with Hypohalites in Alkaline Solution.—In alkaline solution, the halogens are converted into hypohalous acid and hypohalite ions. Hypohalite oxidation is likely to be more drastic than action of the free halogens. Thus, whereas free iodine does not act as an oxidant, hypoiodite is a powerful oxidizing agent. Hypobromite and hypochlorite, in particular, are prone to oxidize primary and secondary alcoholic groups, and to cause cleavage of carbon–carbon bonds; these processes are complicated by the tendency of hypohalites to disproportionate to halate ions [see Eqs. (15) and (16)].

The action of chlorine in alkaline media is much slower than that of bromine. Lewin²⁹ reported that the rate of oxidation of D-glucose at pH 9.8 by hypobromite is 1360 times higher than that by hypochlorite at the same pH. For cellulose, the ratio is much smaller (33 to 1). The complexity of the latter system is, however, revealed by the variability of this ratio over the pH range of 8–13; at pH 6–7, the action of hypochlorite is actually slightly faster than that of hypobromite. Maltodextrins and starch have been oxidized with alkaline sodium hypochlorite. The resulting oxidized polysaccharide formed stable complexes with calcium cations.³⁰

Maximal rates of oxidation of sugars by chlorine and bromine have been observed near neutrality and several studies have been conducted in order to establish the identity of the active oxidant as well as the mechanism of the reaction (Ref. 1, pp. 1116, 1117). As for other related oxidations with halogens, β anomers of glycosides react more rapidly than the α anomer

with hypochlorite at pH 9 and 11. Similarly, the oxidation of β -D-glucopyranose by hypoiodous acid at pH 9.8 is, initially, at least 25 times as fast as that of the α anomer. As the oxidation progresses, the simultaneous mutarotation tends to equalize the two rates.

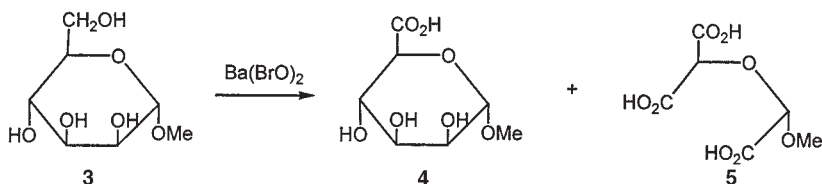
Alkaline hypiodite oxidizes aldoses, under carefully controlled conditions, almost quantitatively to aldonic acids (see preceding chapter). Measurement of the iodine consumed permits quantitation of the amount of aldose originally present [Eq. (19)].



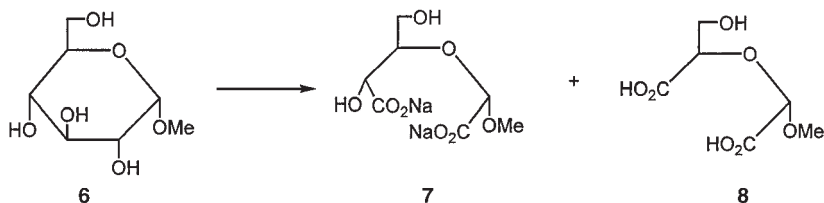
The rate of the competitive reaction, namely the formation of iodate, should be lower than the oxidation of the aldose. Iodide ion suppresses iodate formation; however, too much iodide causes overoxidation by maintaining a higher concentration of oxidant (hypoiodous acid) during the reaction. Hypiodite has been suggested as the reagent of choice for oxidizing fragments from periodate-oxidized polysaccharides to aldaric and lower acids for separation and identification.³¹ Kinetic studies on the oxidation of hexoses and pentoses by iodine in alkaline solution have been reported.³² The results indicated that the active oxidizing species is hypoiodous acid. Maximal oxidation is found at pH 11.2. A mechanism for the oxidation was proposed.

As previously reported (Ref. 1, pp. 1118, 1119) ketoses are essentially inert to the action of hypiodites under the conditions used for the determination of aldoses, and aldoses are converted by hypiodite or hypobromite into glycosiduronic acids in rather low yield. For example, methyl α -D-mannopyranoside (3) afforded methyl α -D-mannopyranosiduronic acid (4), although cleavage of carbon-carbon bonds also occurred to give 5 (Scheme 3).

Alditols are oxidized by alkaline solutions of some halogens, and the main product seems to be the 1,2-dicarbonyl derivative. However, in further studies on the oxidation of pentitols and hexitols with bromine in the presence of calcium carbonate, 2- and 3-uloses and 2,5-hexodiuloses were



SCHEME 3



SCHEME 4

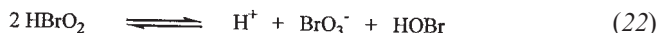
identified by gas chromatography–mass spectrometry of the trifluoroacetylated *O*-methyloxime and *O*-butyloxime derivatives.^{33,34}

Aldonamides having free hydroxyl groups at C-2 are degraded to the aldose having one less carbon atom by treatment with hypochlorites. This is the basis of the Weerman method of degrading aldoses (see Ref. 1, Chapter 3).

Suspended nickel peroxide seems to be the reactive species in the nickel-catalyzed oxidative cleavage of glycals, using sodium hypochlorite as the primary oxidant.³⁵ β -Cyclodextrin (cyclomaltoheptaose) was oxidatively cleaved ($\sim 50\%$) between C-2 and C-3, although oxidation at C-6 ($\sim 25\%$) appeared to occur as well. In contrast, maltodextrin (malto-oligosaccharides) was oxidized at the primary HO function, and methyl α -D-glucopyranoside (6) gave the diacid 7, which was further degraded to 8 (Scheme 4).

2. Halic Acids (HXO₃)

In the presence of a small amount of bromide, acidic bromate oxidations are autocatalytic, and several oxybromo species are present in the reaction mixture,³⁶ according to Eqs. (20)–(22).

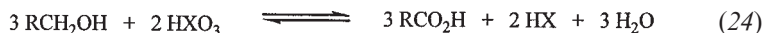


Bromous acid disproportionates rapidly, and at high bromate and acid concentration, a fast equilibrium is established between bromate and hypobromous acid [Eq. (23)].

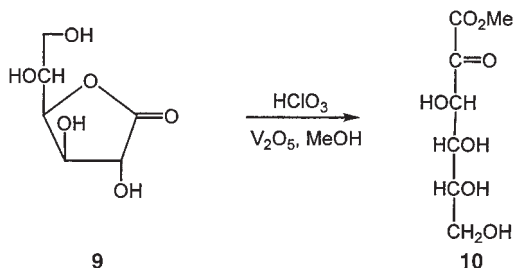


Under these conditions, oxidation by hypobromous acid predominates and autocatalysis is observed with organic substrates. Hypobromous acid oxidizes the substrate and is reduced to bromide, which promotes bromate decomposition. The only role of bromate is to reoxidize the bromide formed in the oxidative step.³⁶

Acidic chlorate oxidations are also carried out with a small amount of chloride, and according to the reaction conditions, different equilibria predominate.³⁷ With these reaction systems, the oxidizing oxyhalogen species, formed *in situ*, promotes the oxidation of the primary alcohol groups of polysaccharides to carboxylic acids.³⁶ Thus, the stoichiometry of the overall oxidation in strongly acidic medium (85% H₃PO₄) is given by Eq. (24).



Chloric acid, in conjunction with catalysts (particularly vanadium pentaoxide), is used for the oxidation of aldonic acids or lactones to the 2-glyculosonic acids. Thus, D-glucono-1,4-lactone (**9**) and potassium D-galactonate in methanol, in the presence of phosphoric acid and vanadium pentaoxide, are oxidized by chloric acid to methyl D-*arabino*-2-hexulosonate (**10**) and methyl D-*lyxo*-2-hexulosonate, respectively.³⁸ At moderate temperatures in the absence of a catalyst, aldoses, ketoses, and sucrose are inert to the action of chlorates over a several weeks time period;³⁹ bromates in alkaline solution also exert no oxidative action (Scheme 5).



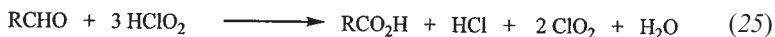
SCHEME 5

3. Chlorous Acid (HClO₂)

Chlorous acid is of particular interest because of its use for the removal of lignin and other noncarbohydrate components from woody tissue without

appreciable action on the carbohydrates (see Ref. 1, Chapter 37). It is also reported to be an effective bleaching agent.

Jeanes and Isbell³⁹ found that, under mild conditions, aldoses are oxidized to aldonic acids, but that nonreducing carbohydrates and ketoses are oxidized only slowly. The rate of oxidation decreases in the order: pentoses > hexoses > disaccharides; however, in contrast to other oxidants, chlorous acid oxidizes α -hexoses more rapidly than the β anomers. The yields of aldonic acids are, however, less than those from bromine oxidations.⁴⁰ The equation for the oxidation in acidic solution was expressed as:



The quantitative stoichiometry of the D-glucose–chlorous acid reaction has been studied in detail; the reagent used was sodium chlorite in a phosphoric acid–phosphate buffer at pH 2.4–3.4. The molar ratio of oxidant consumed to D-glucose consumed was 3:1; no overoxidation occurred over extended periods of time. The method is recommended for the determination of aldehyde groups in carbohydrates, especially alkali-sensitive carbohydrates.

The effectiveness of various chlorine oxidants, and the influence of the pH, on D-galacturonic acid has been studied (see Ref. 1, p. 1120). The autocatalytic chlorite oxidation of polysaccharides is similar to that described for the bromate oxidation (see Section II.2). Thus, the reactive oxyhalogen species are reduced to halides, as shown in Eq. (26).



4. Miscellaneous Halogen Oxidants: *N*-Halosulfonamides and *N*-Halosuccinimides

Whistler and co-workers⁴¹ used chlorine in nonaqueous solvents (acetic acid or carbon tetrachloride) to effect chlorinolysis of glycosides. The initial products of this reaction are a glycosyl chloride and a hypochlorous ester [Eq. (27)].



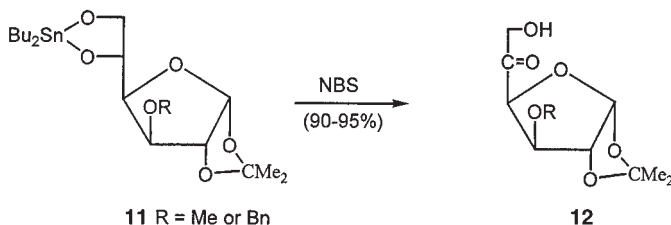
The presence of the glycosyl chloride was demonstrated by its conversion into an ethyl glycoside by ethanol in the presence of a silver salt. The hypochlorite ester formed by chlorinolysis of a methyl glycoside underwent

elimination of hydrogen chloride to give formaldehyde. A similar reaction with amylose produces the chlorinolysis of the 1 \rightarrow 4 links and oxidation of the alcohol group on C-4, via a D-glucose-4-hypochlorite residue. The position of oxidation was proved by sequential reduction and hydrolysis of the product, to generate derivatives of both D-glucose and D-galactose. This reaction is an exception to the generalization that halogens as oxidants do not normally introduce halogen atoms into the compound.

Aromatic *N*-halosulfonamides are a group of mild oxidizing agents which contain the strongly polarized *N*-linked halogens in the +1 state. They undergo a two-electron change to form halide ions and the corresponding sulfonamides. Prominent members of this class of oxidants are *N*-chloro- and *N*-bromo-*p*-toluenesulfonamides (chloramine-T and bromamide-T, respectively). Oxidation of alcohol groups by NBS or *N*-bromoacetamide in acidic medium has been ascribed⁴² to the oxidative attack of H_2BrO^+ species according to Eq. (28). A radical mechanism has also been proposed for the oxidative cleavage of 1,2-diols by *N*-halosuccinimides.⁴³ *N*-Bromosuccinimide (NBS), as well as *N*-bromoacetamide or *N*-bromocarbamide, in methanol, oxidize benzylated sugars to the corresponding aldono-lactones.⁴⁴



Dibutylstannylene acetals of diols (such as **11**) were found to be oxidized regioselectively by NBS to α -hydroxyketones (**12**)⁴⁵ (Scheme 6).



SCHEME 6

The ruthenium-catalyzed oxidation of aldoses by NBS under acidic⁴⁶ and basic⁴⁷ conditions have been investigated. The order of reactivity of some pentoses and hexoses has been determined for their oxidation by NBS in aqueous acidic media containing Hg(II) acetate. A mechanism for the reaction has been suggested on the basis of kinetic measurements.⁴⁸

The oxidation of some hexoses⁴⁹ and pentoses⁵⁰ by *N*-chloroarylsulfonamides in alkaline conditions has been conducted, and the kinetics studied. The products were identified as the corresponding aldonic acids for aldoses, and arabinonic acid for fructose. Further studies⁵¹ indicated that both

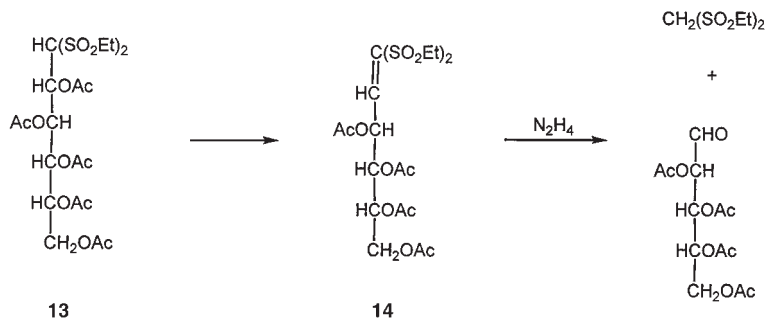
pentoses and hexoses of the *erythro*-series undergo oxidation to a mixture of aldonic acids: arabinonic, ribonic, erythronic, and glyceric. In the case of hexoses, oxidation occurs mainly with the cleavage of the C-1–C-2 and C-3–C-4 bonds, whereas pentoses are oxidized mainly with cleavage of the C-1–H and C-1–C-2 bonds. Based on these data, a mechanism involving the *aldo*-enolic anions of pentoses and *keto*-enolic anions of hexoses has been proposed.

Kinetics of oxidation of four pentoses by bromamide-T were conducted in alkaline medium at different temperatures and the overall activation parameters have been calculated.⁵² Aldonic acids were the oxidation products, and a mechanism was suggested in which formation of the enediol anion of the sugar is the rate-limiting step. As aldoses may undergo epimerization in alkaline solutions, the oxidation of monosaccharides with bromamide-T was also performed in hydrochloric acid solution.⁵³ Kinetic parameters revealed a low reactivity of ketoses relative to aldoses, and indicated that the cyclic forms of the latter are involved in the oxidations.

III. ORGANIC PEROXY ACIDS

Peroxy acids, RCO_2OH , are comparable to hypohalous acids, HOX , in that they possess a good leaving group, RCO_2^- , and so can develop an electrophilic center, HO^+ in the transition state [Eq. (10), $\text{X} = \text{RCO}_2^-$]. Such oxidants are either used as such, or are prepared as needed by the direct addition of hydrogen peroxide to the organic acid in the reaction mixture. Peroxy acids can react with alkanes to give hydroxylated products.⁵⁴ This may be an electrophilic reaction, because the rate increases with increased acidity of the peroxy acid. Dioxiranes are also able to insert an oxygen atom into alkanes.⁵⁵

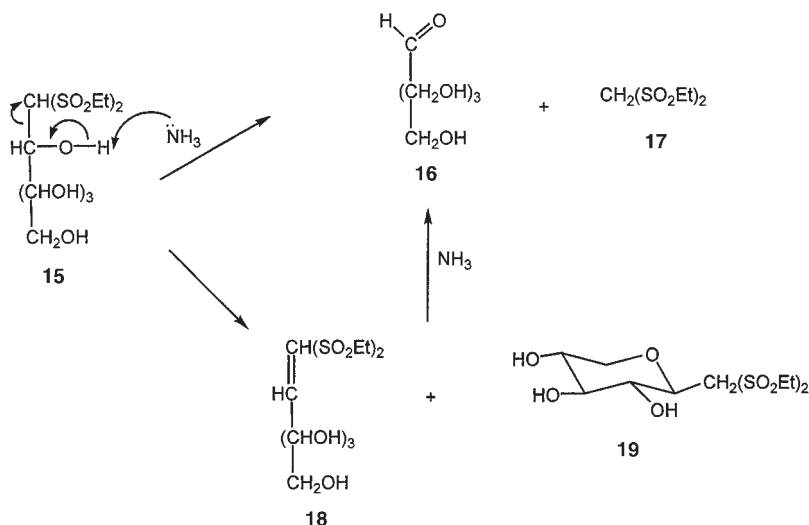
Peroxy acids, as an alternative to permanganate for the oxidation of aldose diethyl dithioacetals to disulfones, were first employed by MacDonald and co-workers.⁵⁶ Thus, D-glucose diethyl dithioacetal pentaacetate (**13**) was oxidized by peroxyphthalic acid in ether to 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1,1-bis(ethylsulfonyl)-D-*arabino*-hex-1-enitol (**14**); this unsaturated disulfone may be cleaved at the double bond by hydrazine to afford arabinose and bis(ethylsulfonyl)methane (Scheme 7). D-Lyxose was similarly prepared. Unacetylated aldose dithioacetals can be converted by the action of aqueous peroxypropanoic acid into disulfone derivatives, which are readily degraded in aqueous ammonia to the corresponding aldose having one fewer carbon atom.⁵⁷ D-Erythrose, D-threose, and D-arabinose were obtained in high yields from the dithioacetals of D-arabinose, D-xylose, and D-mannose. The ring in *scyllo*-*myo*-inosose was broken by oxidation of the dithioacetal and subsequent ammonolysis of both carbon–carbon bonds to



SCHEME 7

the sulfonylated center, affording *xyl*o-pentodialdose. D-Fructose diethyl dithioacetal reacts with peroxypropanoic acid in 1,4-dioxane to afford a (presumably unstable) disulfone which decomposes spontaneously, yielding D-erythrose in a single step.

Hough and Richardson⁵⁸ explored the reaction of unacetylated hexose dithioacetals with peroxypropanoic acid; the sulfone **15** initially formed is only marginally stable, and undergoes dehydration to mixtures of the unsaturated disulfone (**18**) and the 2,6-anhydro-1-deoxy-1,1-bis(ethylsulfonyl)alditol (**19**). All three products are degraded by aqueous ammonia to the next lower sugar (**16**) and bis(ethylsulfonyl)methane (**17**). This degradation is much slower for **18** than for **15**, and it was concluded that hydration of **18** to **15** precedes disproportionation (Scheme 8).

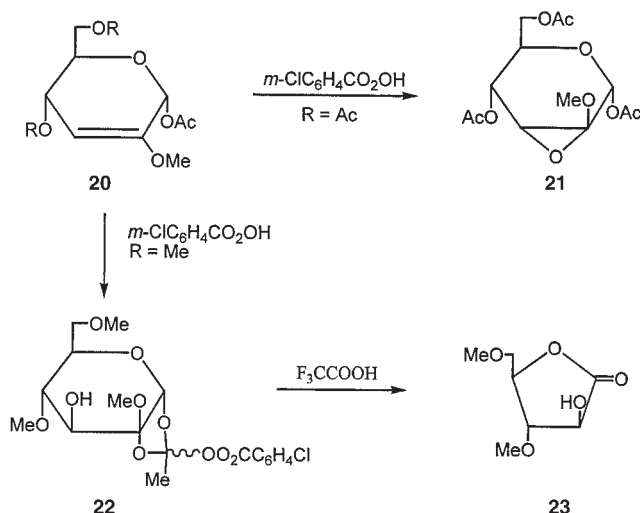


SCHEME 8

The cyclodehydration of **18** to the anhydroalditol derivative **19** has been explained as an attack by the 6-hydroxyl group on the double bond. Studies by Hall *et al.*⁵⁹ of acyclic sulfones formed from two heptose dithioacetals epimeric at C-2 revealed their ready conversion in hot water into a common 2,6-anhydride, which was shown by nuclear magnetic resonance (NMR) analysis to have the bulky bis(ethylsulfonyl)methyl group in the equatorial orientation. The sulfone prepared from D-arabinose diethyl dithioacetal cyclizes to 2,5-anhydro-1-deoxy-1,1-bis(ethylsulfonyl)-D-ribitol.⁶⁰ Horton and Norris reported⁶¹ on a range of synthetic applications of dithioacetals and their oxidation products.

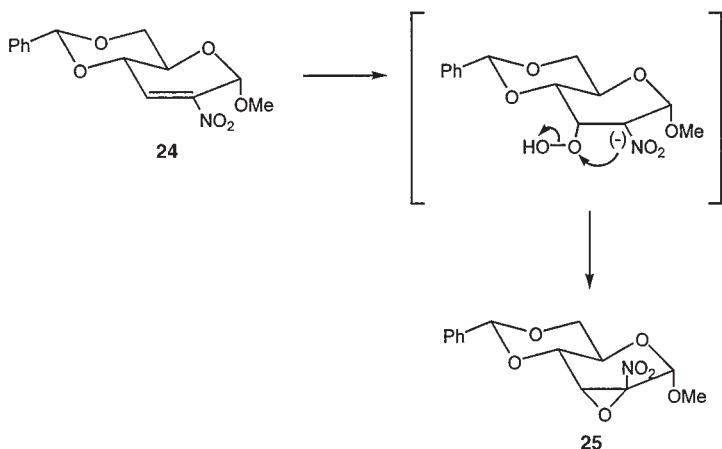
Although peroxy acids as reagents in sugar chemistry have been confined largely to oxidations of dithioacetals, they have also been used in the hydroxylation of alkenes to give dihydroxy derivatives. Such hydroxylation is normally *anti*; the initial epoxide, formed by *syn* addition to the double bond, suffers inversion of stereochemistry in the course of hydrolysis, to generate ultimately an *anti*-glycol grouping.

Aspinall and King⁶² used *m*-chloroperoxybenzoic acid to epoxidize 1,4,6-tri-*O*-acetyl-3-deoxy-2-*O*-methyl- α -D-*erythro*-hex-2-enopyranose (**20**, R = Ac) to the corresponding oxirane **21**, which underwent hydrolysis to afford a hexopyranos-2-ulose derivative as the main product. 1-*O*-Acetyl-3-deoxy-2,4,6-tri-*O*-methyl- α -D-*erythro*-hex-2-enopyranose (**20**, R = Me) reacts with *m*-chloroperoxybenzoic acid to give the mixed orthoperoxy anhydride **22**, which decomposes spontaneously, in the presence of trifluoroacetic acid, to 3,5-di-*O*-methyl-D-arabinonolactone (**23**) (Scheme 9).



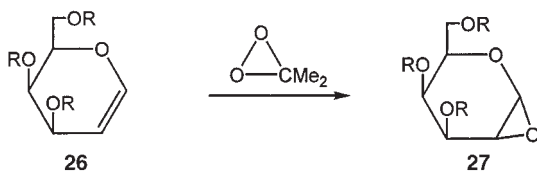
SCHEME 9

Stable epoxides of α,β -unsaturated carbonyl and nitro compounds have been obtained. For example, compound **24** reacts with hydrogen peroxide or alkyl hydroperoxides in the presence of a base to give **25**.⁶³ The reaction is believed to proceed by Michael addition of the hydroperoxide anion to **24**, and subsequent intramolecular displacement of hydroxide by the anion of the carbon atom that bears the nitro group (Scheme 10).



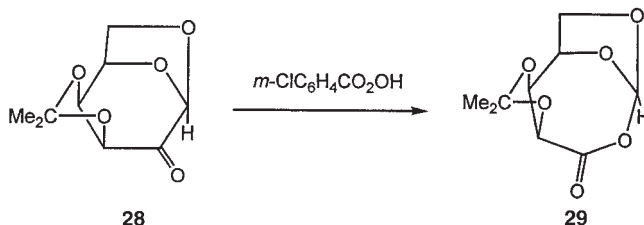
SCHEME 10

Oxidation of glycals with peroxy acids does not lead to isolable epoxides, as the initially formed 1,2-anhydro sugar reacts with the acid derived from reduction of the peroxy acid. However, direct epoxidation of glycals (such as **26**) to 1,2-anhydro sugars (**27**) has been achieved with anhydrous 3,3-dimethyldioxirane.⁶⁴ The byproduct, acetone, does not react with the 1,2-epoxide. Similarly, perfluoro-*cis*-2,3-dialkyloxaziridines effect direct epoxidation of the tri-*O*-acetyl derivatives of D-glucal and D-galactal, and di-*O*-acetyl-L-rhamnal, to give neatly the corresponding 1,2-anhydro sugars with moderate to complete diastereoselection.⁶⁵ Glycals and hex-4-enopyranosides have also been stereoselectively epoxidized with a *m*-chloroperoxybenzoic acid–potassium fluoride complex⁶⁶ (Scheme 11).



SCHEME 11

The Baeyer–Villiger transformation of several protected derivatives having a free ketone group has been effected by *m*-chloroperoxybenzoic acid. Thus, 1,6-anhydro-3,4-*O*-isopropylidene- β -D-*lyxo*-hexopyranos-2-ulose (**28**) was converted into the cyclic, orthoacid anhydride **29**.⁶⁷ As an additional example, the Baeyer–Villiger oxidation of Ferrier carbocyclization products derived from D-glucose afforded 5-deoxyhexofuranosiduronic acids, via the ring-expanded lactonic intermediates⁶⁸ (Scheme 12).



SCHEME 12

IV. PHENYLHYDRAZINE AS AN OXIDANT

Under controlled, acidic conditions, an excess of phenylhydrazine acts specifically to convert the (usually terminal) --CO--CHOH-- grouping in aldoses or ketoses into a bis(phenylhydrazone) residue, which undergoes ready hydrolysis to liberate a --CO--CO-- grouping. Simultaneously, reductive cleavage of the nitrogen–nitrogen bond of the oxidant gives aniline and ammonia as products. As the applications of phenylhydrazine as a net oxidant have been described in detail in the second edition of “The Carbohydrates” (Ref. 1, pp. 1125, 1126) and also several aspects on the chemistry of bis(phenylhydrazones) are treated in the preceding chapter and in Chapter 21 of Ref. 1, no further discussion on this subject is included here.

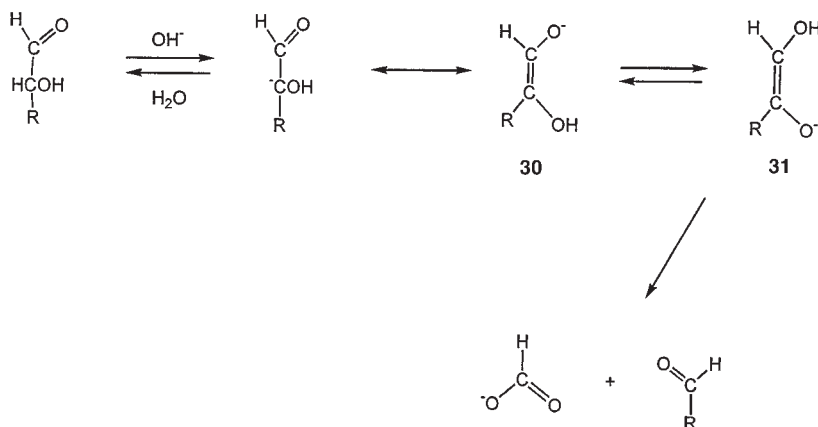
V. OXYGEN IN ALKALINE AND NEUTRAL SOLUTION

Study of the action of molecular oxygen on sugars is of considerable interest insofar as it relates to the mechanism of the *in vivo* oxidation of sugars; the influence of configurational and conformational features on the course of catalytic oxidations is an intensively studied topic. Molecular oxygen has synthetic utility for the degradation of sugars to acids having

shorter chains. The catalytic oxidation of carbohydrates and related compounds by oxygen and hydrogen peroxide has been recently reviewed.⁶⁹

1. Oxidation in Alkaline Solution

In alkaline solution, oxygen degrades aldoses to aldonic acids having one fewer carbon atom. Air or oxygen may be used, and relatively high yields of acids are obtained.⁷⁰ Ketoses act similarly; oxidation of L-sorbose affords L-xylo-2-hexulonic acid plus L-xylonic acid in good yield. The formation of the reaction products has been rationalized by assuming ionization of the aldoses or ketoses to intermediate enediols (**30**, **31**) by the action of the base, followed by the radical or ionic addition of oxygen. The intermediate 2-glyculosonic acid gives the next lower aldonic acid by decarboxylation (Scheme 13).



SCHEME 13

3-*O*-(α -D-Glucopyranosyl)-D-arabinonic acid and its β anomer were prepared by oxidation of maltose and cellobiose, respectively;⁷¹ 3-*O*-(β -D-galactopyranosyl)-D-arabinonic acid is formed similarly from lactose.

In its ground state, the oxygen molecule exists as a diradical; it is a stable molecule in isolation, and its reactivity is greatly enhanced in the presence of catalysts. In alkali-catalyzed autooxidation, fragmentation of carbon-hydrogen bonds is either caused or greatly facilitated by alkali; subsequent transfers of electrons are relatively rapid and facile processes.

The reaction of oxygen with cellulose in alkali (autooxidation or alkaline aging) was interpreted as being a free-radical process (see Ref. 1, p. 1127) initiated by loss, from an activated molecule (for instance, an enol), of a

labile hydrogen atom, followed by capture of oxygen by the radical to generate a hydroperoxy radical. Abstraction of a hydrogen atom from the substrate (RH) would afford the radical R•, which is propagated in a chain reaction. The hydroperoxides formed can decompose in various ways to give an oxidation product, or to produce oxy radicals that can react with molecules of RH, thus accelerating its oxidation.

For the oxidative degradation of D-glucose, Bamford and Collins⁷² proposed that oxygen adds to the enediol anion, forming a hydroperoxide intermediate that decomposes to arabinonic and formic acids. However, the direct combination of the carbanion with oxygen is considered to be a highly improbable initiation process; Russell⁷³ pointed out that such a step would require bond creation and a change in multiplicity (a spin-forbidden process). Similarly, an ionic mechanism based on hydride transfer from a doubly-ionized aldehydrol group, and subsequent attack by a hydroperoxyl anion, incorporates a step similar to the one disputed by Russell.

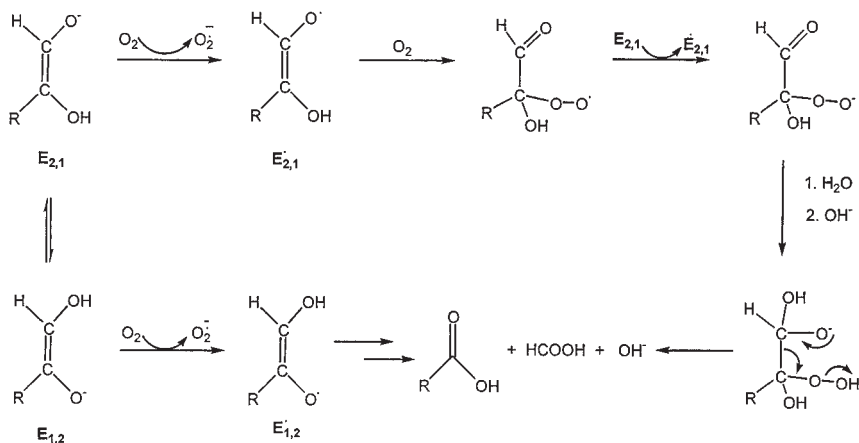
Gersmann *et al.*⁷⁴ suggested another mode of initiation, which proceeds by deprotonation of RH to a carbanion that transfers one electron to an oxygen molecule; capture of oxygen produces a peroxy radical that oxidizes another molecule of the initial carbanion, the last two steps constituting a chain-propagation process. In hydrocarbon oxidations, Russell⁷³ also showed that reactions of carbanions with O₂ proceed via a two-step one-electron transfer pathway [Eqs. (29)–(32)].



Further studies verified the intermediate formation of free radicals, as demonstrated by the electron-spin resonance spectra obtained during autooxidation of cellulose,⁷⁵ and hydrogen peroxide was identified as a byproduct in the autooxidation of D-glucitol. Similar oxidations of cellulose in the presence of alkenic monomers afforded graft copolymers. The autooxidation of cellulose and of the cello-oligosaccharides was shown to be more extensive in the presence of transition-metal cations.

Vuorinen⁷⁶ demonstrated by ¹⁷O₂ labeling experiments that cleavage of the enediol anion proceeded via the C-1 and C-2 hydroperoxides in a 1:2

ratio. Sheldon *et al.*⁶⁹ suggested a general mechanism for the oxidation of aldoses in alkaline media that takes into account the rapid equilibrium between the enediolates $E_{1,2}$ and $E_{2,1}$. This equilibrium was combined with the Russell mechanism of reaction with O_2 to form peroxy-radicals, which in consecutive steps underwent cleavage. This mechanism does not require a spin-forbidden addition of triplet oxygen to the enediol anion (Scheme 14).



SCHEME 14

The formation of monohydroxy acids having chains of four, three, or two carbons can be rationalized with the same mechanism of oxidation of the corresponding enediol. The 1,2-enediol can rearrange to the 2,3- or 3,4-enolates, which undergo the oxidative cleavage. Alternatively, the enediol may undergo a retro-aldol condensation followed by oxidation.

Although these alkali-catalyzed oxidative degradations are interesting from the mechanistic point of view, they cannot be controlled and hence, they do not find preparative use.

2. Catalytic Oxidation

In the presence of platinum catalysts, the main process effected on sugars by oxygen is dehydrogenation.⁷⁷ Isotopic oxygen is not incorporated into the organic product, and the dehydrogenation is not reversible in the presence of $H_2^{18}O$. The oxidation seems to be a radical process, with initial

attack on a C–H bond [Eq. (4)]; the stability of the resulting radical is the important factor [Eq. (5)]. As with platinum, such related metals as palladium and rhodium are effective catalysts for oxidation of alcohols. Such oxidations in the carbohydrate field have been reviewed.^{69,77}

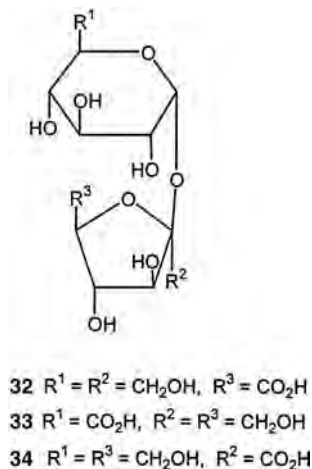
As the catalytic oxidation occurs on a catalyst surface, it is profoundly influenced by steric effects: (a) oxidation of the anomeric position of aldoses takes place selectively to give the corresponding aldonic acids; (b) when the anomeric position is protected, as in glycosides, or it has been reduced to an alditol, primary alcoholic groups are generally oxidized rather than secondary alcoholic groups; (c) when only secondary hydroxyl groups on a pyranoid ring are available, the favored attack is on a carbon atom bearing an axially attached hydroxyl group; and (d) in the case of rigid, bicyclic molecules, the favored attack is on the carbon atom bearing an *endo* hydroxyl group.

Platinum-catalyzed oxidation of D-glucitol affords L-gulose and D-glucose. The specificity of this reaction is probably due to both statistical and steric factors. A related example is the conversion of L-sorbose into L-xylo-2-hexulosonic acid in 62% yield (see Ref. 1, p. 1129). Similar oxidation of 1,2-acetals of α -D-glucofuranose and α -D-xylofuranose affords the respective glycuronic acids whereas, under more drastic conditions, the former acetal is converted into 1,2-*O*-isopropylidene- α -D-xylo-hexofuranos-5-ulosono-6,3-lactone, a synthetic precursor of ascorbic acids.

This method of oxidation has been extensively used in the preparation of alkyl and aryl glycopyranosiduronic acids,⁷⁷ and it has also been applied to the oxidation of other glycopyranosides, aldopentofuranosides, disaccharides, and polysaccharides. Also, several examples have been given¹ showing that the oxidation of axially attached secondary alcoholic groups occurs preferentially when primary alcoholic groups are either absent or protected. In correlation with the attack on the equatorially attached hydrogen atoms of the (axial) alcohol groups, several glycoside derivatives have been oxidized. Similarly, oxidation of a series of partially protected acetals of ketoses revealed that primary hydroxyl groups react faster than axial secondary hydroxyl groups, that proximity to the ketogenic center slows the reaction of the former more than the latter, and that equatorial secondary hydroxyl groups are almost inert. The favored oxidation of axial hydroxyl groups was also demonstrated for anhydro sugars and anhydrohexitols. The Pt–C-catalyzed oxidation of 1,4;3,6-anhydro-D-glucitol in aqueous solution brought about conversion of both free hydroxyl groups into carbonyl functions.⁷⁸

The oxidation of D-glucose 1-phosphate and analogues to the alduronic acid 1-phosphates by molecular oxygen over Pt on carbon occurred with

oxidation of secondary HO groups and subsequent C–C bond cleavage as side reactions. These side reactions are retarded by substituents at C-5, and the protecting ability follows the order $\text{CO}_2^- > \text{CH}_2\text{OH} > \text{H}$.⁷⁹ The Pt–C-promoted oxidation of sucrose by oxygen at 100 °C and neutral pH proceeded with high selectivity for the oxidation of HO-6 and HO-6', with no evidence for reaction at HO-1.^{80,81} Oxidation of sucrose by an alternative procedure, in oxygen-saturated aqueous solution, with the pH adjusted by addition of NaCO_3H , led to sucrose monocarboxylic acids with a selectivity of 96%. The three primary CH_2OH groups are converted in a 10:9:1 ratio [C-6 fructose (**32**), C-6' glucose (**33**), C-1 fructose (**34**)], correlating with the accessibility of each group to the Pt surface⁸² (Scheme 15). Methyl α -D-fructofuranoside was oxidized with O_2 –Pt (C), at 60 °C and pH 9, to methyl α -D-arabino-hex-2-ulofuranosiduronic acid, with 83% selectivity. Oxidation of inulin under the same conditions led to only partially oxidized products (20% of the primary hydroxyl groups). Adsorption and desorption phenomena appear to play an important role during the oxidation process.⁸³



SCHEME 15

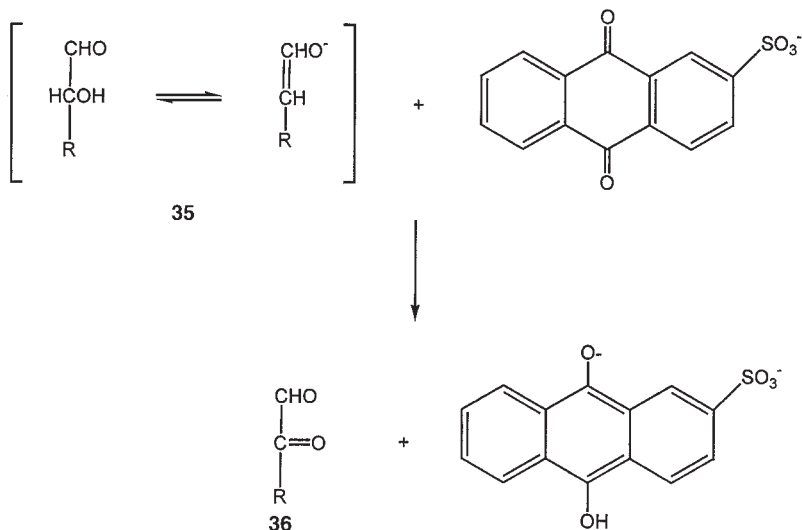
As with platinum, the palladium-catalyzed oxidation of anomeric hydroxyl groups in aldoses is a rather selective process.⁸⁴ The influence of pH in the Pd-catalyzed oxidation of glucose has been studied. It was observed that the gluconic acid formed, in its free form, reversibly inhibits the oxidation process in acidic media.⁸⁵ The oxidation of D-glucose has been performed with palladium-on-alumina and with bismuth-containing palladium-on-charcoal in water.⁸⁵ The selectivity in the air oxidation of

aqueous D-glucose and D-gluconate has also been examined, with Pt catalysts supported on activated charcoal, with or without such promoters as bismuth or gold. The combined use of such heavy metals as bismuth, together with Pt or Pd, introduced an important improvement in the selectivity of these catalytic oxidations. Thus, the use of Pd, or both Pd and Pt catalysts, doped with bismuth,⁸⁶⁻⁸⁸ led to an enhancement in the selectivity of the oxidation. An additional advantage of these catalysts is that their susceptibility to poisoning by molecular oxygen is strongly diminished, making the oxidations more efficient. These processes are useful for the oxidation of D-glucose and various mono-, di-, and oligo-saccharides on the industrial scale.

The oxidation of secondary hydroxyl functions to the carbonyl group is often an undesired side reaction. However, the oxidation of D-gluconic acid to "2-oxogluconic" acid is a highly selective process (97% yield) when a Pt-Bi catalyst is employed.⁸⁹ Such a procedure is of industrial interest.

The so-called pyrochlore oxides are mixed metal oxides which have high surface areas. They have been prepared as combinations of ruthenium-bismuth and ruthenium-lead.⁹⁰ Exposure of methyl α -D-glucopyranose in aqueous solution (0.7 M KOH) at 50–75 °C to oxygen at 10–20 bar in the presence of bismuth-rich ruthenium pyrochlore oxide caused glycol cleavage to give the C-2,C-4-dicarboxylate with the concomitant formation of formate. On prolonged reaction, the primary hydroxyl group was also oxidized to carboxylate.⁹¹ Cyclomaltoheptaose (β -cyclodextrin) reacted nonselectively, and the catalyst does not seem to be suitable for the controlled oxidation of starch.⁹²

The kinetics have been studied of the alkali-catalyzed oxidation of D-glucose with sodium anthraquinone-2-sulfonate in aqueous ethanol. At high concentration of the quinone, the rate-determining step for the oxidation is the enolization of D-glucose, to give the intermediate **35** and hence "D-glucosone" (D-arabino-hexos-2-ulose, **36**) as the primary product⁹³ (Scheme 16). The quinone is a better acceptor than oxygen of a single electron from the enediol. The resulting radical, itself or combined with O₂ via a peroxide, gives the aldulosule. This product is not further oxidized by the quinone, but if H₂O₂ is added, oxidative degradation of the glycosule to the aldonic acid and formate takes place. Thus, lactose is degraded by this procedure to β -D-galactopyranosyl-(1 \rightarrow 3)-D-arabinonate in 90–95% yield, whereas the classical oxidative degradation with O₂ in alkali gives the same product in only 75–80% yield. A mechanism for the highly selective oxidative degradation of carbohydrates by sodium anthraquinone-2-sulfonate and H₂O₂ (Spengler-Pfannenstiël oxidation) has been proposed⁹⁴.



SCHEME 16

3. Oxidation Under Neutral Conditions

Under conditions simulating biological processes (neutral, aqueous solutions at a temperature of 37.5 °C), oxygen attacks D-glucose, glyceraldehyde, glycerol, and related polyols. One mole of carbon dioxide is formed per mole of D-glucose; sodium ferropyrophosphate has been used as the catalyst. D-Fructose is much more sensitive than D-glucose in the presence of phosphate or arsenate as the catalyst, and the rate of oxidation depends on the concentration of salt present. The action of oxygen on disaccharides and polysaccharides, as well as some aspects of the mechanism of these oxidations has been previously reported (Ref. 1, p. 1131). Further studies have shown that the oxidation of D-xylose, D-glucose, D-glucitol, cellulose, and dextran by oxygen at 170–230 °C affords relatively high yields of acetic and formic acids; increased yields were obtained by addition of iron(II) sulfate as catalyst.⁹⁵

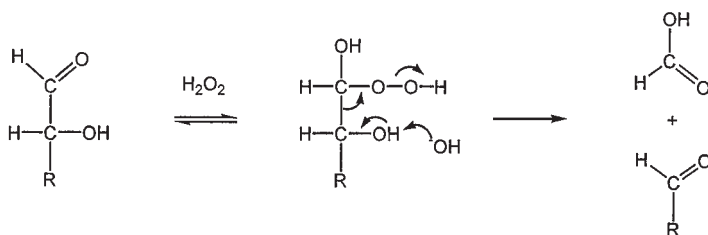
The aqueous oxidation of D-[1-¹⁴C]glucose and D-[6-¹⁴C]glucose at 100 °C afforded formic, acetic, and glycolic acids, and carbon dioxide. The last is mainly produced from C-2 to C-5, the formic acid from C-1, and the acetic acid from C-6.⁹⁶ Addition of aluminum(III) chloride greatly increased the yield of carbon dioxide. Oxidation of D-glucose and D-fructose, studied with ¹⁸O-enriched oxygen, showed that they decompose via the C-1 and C-2 hydroperoxides to give D-erythronic acid as the main product.⁷⁶

VI. HYDROGEN PEROXIDE

Hydrogen peroxide is an ineffective oxidant in polar solvents at acidic or neutral pH, as the formation of a hydroperoxide ion is quite difficult [Eq. (33)]. When the pH is increased, the equilibrium that exists in neutral H_2O_2 solutions is shifted to the right [Eq. (34)].



In alkaline solutions, hydrogen peroxide is used as a bleaching agent; its initial action on cellulose and on amylopectin⁹⁷ is depolymerization. Oxidation seems to occur mainly on reducing end-units and other partially oxidized positions; the (strongly nucleophilic) hydroperoxide anion is more likely to attack the polarized carbonyl than alcohol groups (see Scheme 17). Isbell and co-workers showed that alkaline peroxide degrades aldoses,⁹⁸ ketoses,⁹⁹ and reducing disaccharides¹⁰⁰ sequentially to formic acid, by a series of enolization and oxidation processes. Together with glycuronic and glycolosonic acids, oxalic acid and also formic acid are obtained as products.¹⁰¹ Hydroperoxide intermediates have been proposed in the oxidation of methyl β -D-glucopyranoside.¹⁰²

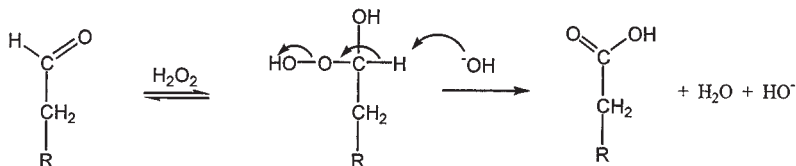


SCHEME 17

In the case of 2-deoxyaldoses, where no hydroxyl group is present at C-2, the α -hydroxy-hydroxyperoxide cleavage is not possible and a different pathway affords the 2-deoxyaldonic acids,¹⁰³ as shown in Scheme 18.

Many other degradation mechanisms (which are not described here) have been proposed by Isbell and Frush¹⁰⁴ in order to account for the various oxidation products formed from carbohydrates by the action of H_2O_2 .

Since traces of heavy metals and metal ions catalyze the decomposition of H_2O_2 into water and oxygen, stabilizers can be added to the solution of H_2O_2 . Such chelating agents as EDTA, are effective for the stabilization of H_2O_2 . Thus, the degradation of aldoses by aqueous alkaline H_2O_2 was



SCHEME 18

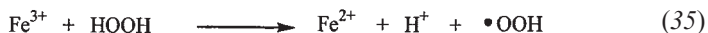
rendered much more selective upon addition of EDTA, in the presence or absence of borate ions. Under these conditions galactose, lactose, maltose, and cellobiose were each converted into the next lower aldoses and formic acid, in high yield.¹⁰⁵

The effect of borate is to form esters with hydroxyl groups of the carbohydrates, which impedes degradation during the oxidation. In this reaction it is essential for the HO groups at C-2 and C-3 to be in *threo* relationship.^{105,106} In contrast to the classical oxidative degradation of lactose, protection against overoxidation by borate results in a good yield (>70%) of “galarose.” Likewise, cellobiose, maltose, and galactose were successfully degraded to the next lower aldoses in the presence of borate ions.¹⁰⁷

Use of catalysts, generally ferric or ferrous salts, promotes radical reactions with hydrogen peroxide; the oxidizing action produced by the ferrous ions is more vigorous.

1. Hydrogen Peroxide and Ferric Ions

Ferric ion catalyzes the formation of the hydroperoxyl radical, according to Eq. (35); such a radical appears to constitute the oxidant in the Ruff method of degrading aldonic acids to the next lower aldoses. A number of examples of the use of this reagent in the laboratory are given in a review article by Moody.¹⁰⁸ The hydroperoxyl radical, which is not so effective an oxidant as the hydroxyl radical, does not attack aliphatic alcohols; accordingly, a substantial yield (about 50%) of the aldose is obtained from the higher aldonic acid. In the presence of an excess of hydrogen peroxide, however, the accumulation of ferrous ions in solution catalyzes the production of hydroxyl radicals and lowers the yield of aldose [see Eq. (36)].

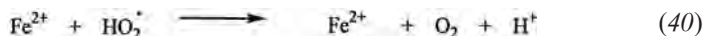
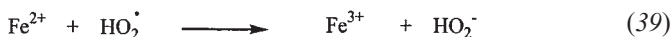
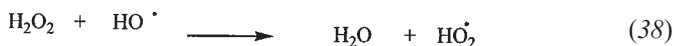
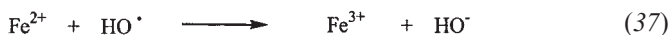
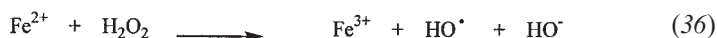


A possible mechanism for this reaction suggests the formation of a carboxyl radical, which undergoes degradation to liberate CO₂. The resulting radical produces the corresponding next lower aldose plus H·.

Hydrogen peroxide in acetonitrile has been shown to convert a pentofuranosidulose oxime into the corresponding nitro derivative.¹⁰⁹

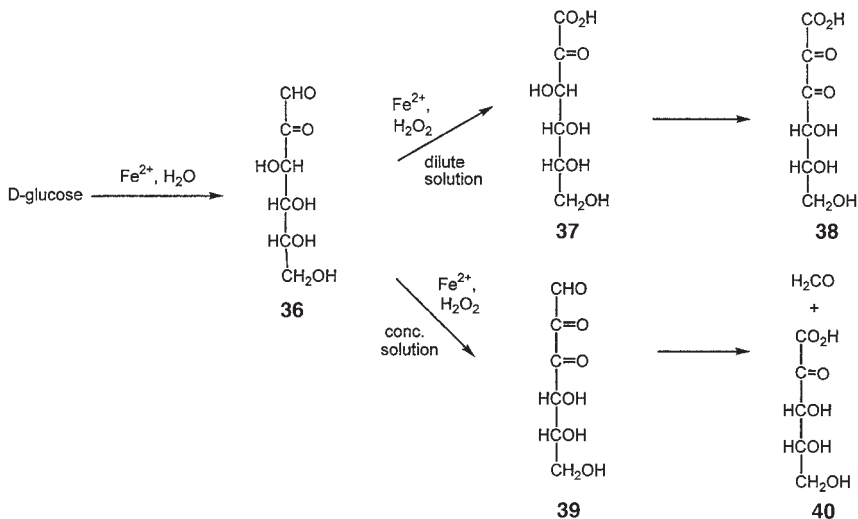
2. Hydrogen Peroxide and Ferrous Ions

The Fenton reagent is a mixture of hydrogen peroxide and a ferrous salt, which leads to the formation of hydroxyl radicals, according to Eqs. (36)–(40). Hydroxyl radicals are very effective in abstracting hydrogen atoms, in contrast to the weaker action ascribed (Section VI.1) to hydroperoxyl radicals.



Studies by electron-spin resonance spectroscopy showed that the reaction of hydroxy radicals with carbohydrates produces new radicals via hydrogen abstraction from a C–H group. When such carbohydrates as glucose are substrates, the H^\bullet abstraction from a C–H bond is relatively nonselective, and all six possible radicals can be formed. The fate of these radicals is strongly influenced by the type of starting sugar and by the species present in the reaction medium. All of these aspects have been discussed in the review article by Sheldon *et al.*⁶⁹

At low temperatures, D-glucose and D-fructose in the presence of ferrous sulfate are converted into D-arabino-hexos-2-ulose (**36**), which can be degraded by further oxidation to glycolic acid, glyoxylic acid, and D-erythronic acid. The nature of the products formed under various conditions and the mechanism of the reaction have been described (see Ref. 1, p. 1133). In dilute solution, in the presence of ferrous sulfate at low temperature, compound **36** gave D-arabino-2-hexulosonic acid (**37**) and D-erythro-hexo-2,3-diulosonic acid (**38**). In concentrated solutions, formaldehyde was also found. The formation of these products at low temperature was ascribed to the series of reactions in Scheme 19.



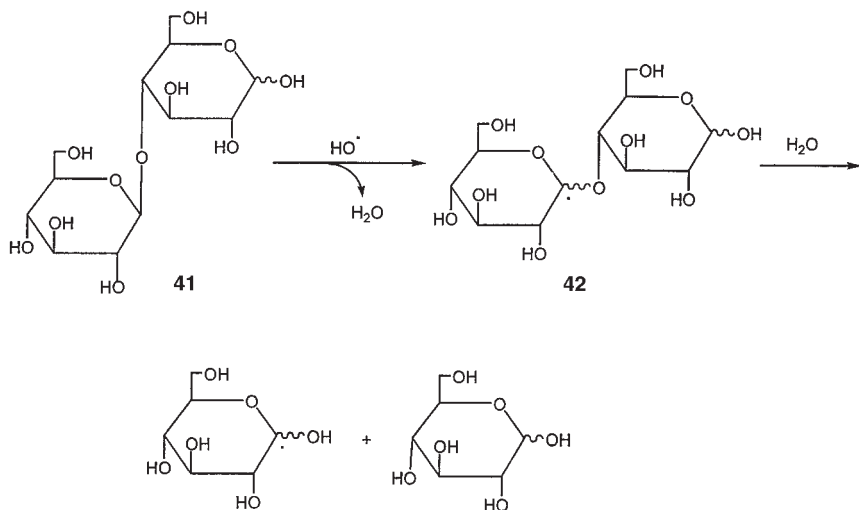
SCHEME 19

At higher temperatures, carbon dioxide, formic acid, oxalic acid, glycolic acid, hydroxymalonic acid, glyceric acid, and other acids were shown to be formed. The formation of carbon dioxide is ascribed to decarboxylation of **38**; oxalic acid and D-erythronic acid arise from cleavage of the C-2–C-3 bond; compound **39** is cleaved to glyoxylic acid plus D-erythronic acid. Compound **40** is oxidized further to D-glycero-2,3-pentodiulosonic acid and is subsequently cleaved to oxalic and glyceric acids.

The degradation of “2-deoxyribose” by Fenton’s reagent has been conducted in acidic, neutral, and alkaline media, and in the presence and absence of hydroxyl-radical scavengers. It seems that both the substrate and the scavengers interact with the metal ions.¹¹⁰ Traces of Fe(II) accelerate the oxidation of carbohydrates by H_2O_2 , but larger quantities of such a cation has a retarding effect.¹¹¹

Primary alcoholic groups are oxidized to aldehydes by the action of peroxide and ferrous ions. The action of the Fenton reagent on 3,4-di-O-methyl-D-mannitol gives (among other products) the products of demethylation, indicating that the hydroxyl radical attacks the C–O–Me grouping as well as primary alcoholic carbon atoms.¹¹² Oxidation of 1 mol of methyl β -D-glucopyranoside with 1.5 mol of hydrogen peroxide in the presence of ferrous ion gives small proportions of pyranosiduloses and D-glucose; undetermined amounts of D-erythronic and D-arabinonic lactones were also formed.¹¹³ The products of degradation of cellobiose (**41**) under Fenton’s conditions have been analyzed by liquid chromatography,

which showed that D-glucose and organic acids were the main products.¹¹⁴ The formation of D-glucose could be due to the abstraction of hydrogen from the anomeric carbon of cellobiose (**41**) to give **42**, which underwent hydrolysis (Scheme 20).



SCHEME 20

VII. NITRIC ACID, NITROGEN DIOXIDE, AND NITROXYL RADICALS

Nitric acid is a strong acid and is a potent oxidant, but its salts are rather unreactive. Under strongly acidic conditions, it converts primary alcoholic and aldehydic groups into carboxylic acid groups. Frequently, however, cleavage of carbon–carbon bonds occurs. Conversion of D-galactose into (insoluble) galactaric (“*mucic*”) acid occurs to the extent of > 70%, and the reaction may be used for the quantitative determination of this sugar.¹¹⁵ Aldoses are oxidized by nitric acid to aldonic and aldaric acids or their lactones (see Ref. 1, pp. 1136, 1137). D-Glucose, for example, is oxidized by nitric acid to D-gluconic acid and D-glucaric acid. Alditols are oxidized to aldonic acids; oxidation of glycerol gives DL-glyceric acid. Aldonic acids are oxidized to 2-glyculosonic acids, aldaric acids, and glycuronic acids. Among the products of the oxidation of D-fructose are formic acid, oxalic acid, erythraric acid, and glycolic acid, but the reaction seems to require more severe conditions than for D-glucose; at low temperature, the ketoses are not attacked by 32% nitric acid.

Oxidation of methylated sugars with nitric acid was used extensively by early workers for locating the position of unsubstituted hydroxyl groups.¹¹⁶ Cleavage of carbon-carbon bonds appears to be facilitated by the presence of such catalysts as vanadium salts. As hot nitric acid acts as a hydrolyzing agent as well as an oxidant, oligo- and poly-saccharides may be used directly.

The reaction probably proceeds via the cyclic forms of the sugars and lactones, as equilibria between the various cyclic forms and the acyclic form are presumably established rapidly under the strongly acidic conditions of these oxidations. Thus, D-galactose undergoes oxidation to (acyclic) galactaric acid, whereas similar reaction of D-mannose affords a dilactone (see preceding Chapter).

The specificity of the oxidation may be enhanced by the use of nitrogen dioxide (NO₂) instead of nitric acid.¹¹⁷ In gaseous form, or in nonaqueous solution, this reagent exhibits a marked specificity for the oxidation of primary alcoholic (and aldehydic) groups; it converts glycosides into glycuronic acids, and cellulose into a D-glucuronan. Nitrogen dioxide has been recommended as an inexpensive oxidizing agent for the production of oxalic acid from carbohydrates.¹¹⁸

The oxidation and subsequent hydrolysis of starch to α -D-glucofuranurono-6,3-lactone has been studied; nitric acid alone, or in combination with nitrites, and nitrogen dioxide, have been examined as oxidants. Good results were obtained for oxidations with nitric acid in the presence of formic acid. A number of patents have been issued on these topics (Ref. 1, pp. 1137, 1138). Treatment of methyl β -D-glucopyranoside with liquid nitrogen dioxide for 5 h at 12°C afforded mostly D-glucaric acid, and three isomeric hexopyranosiduloses accounted for an additional 6% of the products.¹¹⁹

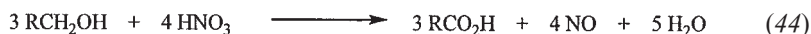
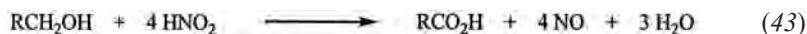
Concentrated nitric acid encounters an initial induction period as an oxidizing agent, and it exerts no oxidizing action in the presence of urea, which removes nitrous acid. The induction period is eliminated by the addition of fuming nitric acid, oxides of nitrogen, nitrous acid, or various other compounds.¹¹⁵ Nitrogen dioxide requires the presence of water for its oxidizing action. These observations indicate that the true oxidant is not nitric acid, but that the effective agent is nitrous acid, which is formed in aqueous solutions of nitric acid or nitrogen dioxide according to the following equilibria:



Under conditions simultaneously favorable for these equilibria and unfavorable for carbon-carbon bond cleavage, the specificity of the reaction is greatly increased. Oxidation of primary alcohol groups appears to proceed through the intermediate formation of an ester of nitric (or nitrous) acid.

An improvement of the oxidation of polysaccharides by nitrogen oxides with respect to the degree of oxidation and the molar mass distribution of the products, can be made by dissolving the substrate in 85% phosphoric acid and adding an stoichiometric amount of sodium nitrite as oxidant.¹²⁰⁻¹²² The oxidizing nitrogen oxides are formed *in situ* from nitrite. However, the oxidation is not completely selective and some ketones are produced through oxidation of secondary hydroxyl groups.

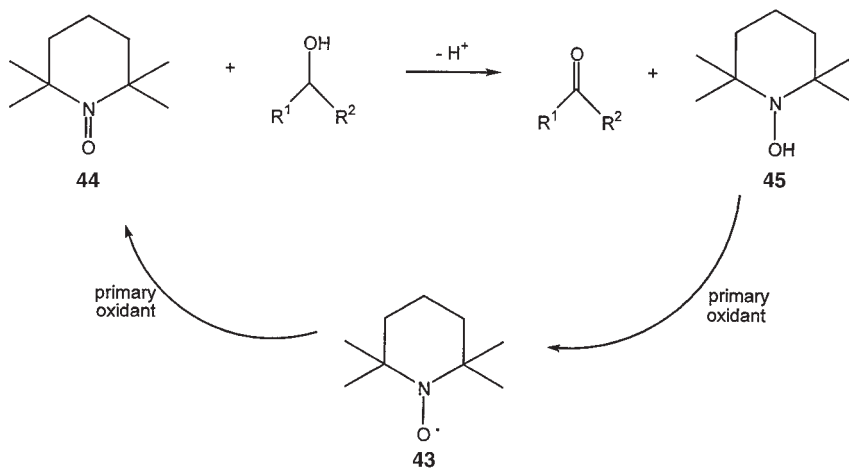
An advantageous variant of the oxidation of polysaccharides by nitrogen oxides in 85% phosphoric acid consists in the use of sodium nitrate, instead of sodium nitrite, as the stoichiometric oxidant and a catalytic amount of sodium nitrite to decrease the induction time.¹²³ The advantage of this variant may be seen by taking into account the stoichiometry of the overall reactions:



For the oxidation of primary hydroxyl groups, three times the amount of nitrite is required when compared with nitrate, and three times as much of the toxic NO would be formed. This oxidation procedure has been applied to the glucans cellulose, amylose, and pullulan. A study of this system with cyclomaltoheptaose (β -cyclodextrin) showed that the reaction is autocatalytic.

Stable organic nitroxyl radicals are of relatively recent use as catalysts in the oxidation of alcohols. Nitroxyl radicals are compounds that contain the *N,N*-disubstituted NO-group with one unpaired electron, and their uses have been reviewed.¹²⁴ The most simple radical of this class is 2,2,6,6-tetramethylpiperidin-1-oxyl (**43**, TEMPO). It is generally assumed that the active oxidizing species, the oxoammonium salt (**44**), is formed in a catalytic cycle by a one-electron oxidation of the nitroxyl radical by a primary oxidant [two-electron oxidation of the hydroxylamine (**45**) is also possible, depending on the primary oxidant] (Scheme 21).

In the "classical" method, sodium bromide is needed to catalyze the formation of **44**, and other primary oxidants, mainly NaOCl, have been employed.¹²⁵ The TEMPO reagent has also been regenerated by



SCHEME 21

electrochemical oxidation.¹²⁶ The system NaOCl–TEMPO has been efficiently used for the oxidation of partially protected or unprotected mono-, oligo-, and poly-saccharides.^{125,127} The oxidation of sucrose by NaOCl–TEMPO, with or without the addition of NaBr as cocatalyst, is accelerated by sonication. The three primary groups of sucrose are oxidized to carboxylic acids.¹²⁷ The rate-controlling step of the reaction was found to be the oxidation of the primary hydroxyl groups by the nitrosonium ion. The chemoselective oxidation of primary alcohol groups of malto-oligosaccharides (maltodextrins) with the ternary oxidation system NaOCl–NaBr–TEMPO was shown to be strongly pH dependent.¹²⁸ Oxidation of polysaccharides is best achieved at pH 9.5 in order to minimize depolymerization, whereas oxidation of oligo- and mono-saccharides requires more strongly alkaline conditions. Thus, D-glucose was oxidized in high yield (>90%) to D-glucaric acid under strongly basic conditions (pH > 11.5). In the absence of NaBr as cocatalyst, the oxidation of starch and methyl α -D-glucopyranoside required high temperatures.¹²⁹

VIII. CHROMIUM(VI)-BASED OXIDANTS

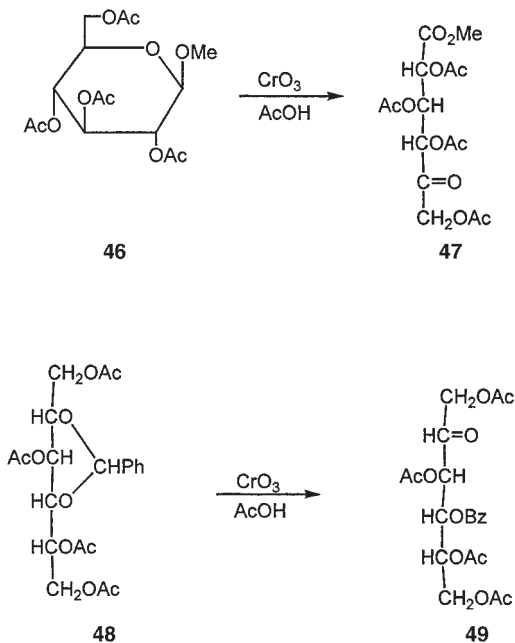
Oxides and oxyacids of Cr(VI) are powerful oxidants. The oxidative power of chromic acid is comparable to that of nitric acid. Chromic esters have been proposed as intermediates in these oxidations, thus isopropyl chromate has been isolated and converted into acetone by pyridine-catalyzed elimination in benzene solution [Eq. (2)]. Decomposition of the chromate ester involves removal of the proton attached to the

oxygen-bearing carbon. At least two mechanisms have been suggested for this step (see Ref. 10, p. 223) and an alternative proposal⁷ involves the formation of a coordination complex that decomposes to radical species, which are further oxidized to products. Mechanistic studies are difficult because the oxidation of alcohols with Cr(VI) is a complex reaction that is influenced by the solvent, the acidity of the reaction medium, the structure of the alcohol, the temperature, and other factors.

Chromic acid (chromium trioxide) is a more generally useful oxidant than either nitric acid or permanganate, because it is stable in organic solvents. Oxidation of alcohols by chromic acid is much faster in acetic acid than in mineral acids of the same concentration; this higher rate has been ascribed either to the decrease in dielectric constant, which favors ester formation, or to formation of the more-reactive acetic chromic anhydride. *tert*-Butyl chromate has been used as an oxidant in acetic acid or in acetic acid–benzene; it acts by rapid transesterification to oxidize primary and secondary alcohols. Mixtures and complexes of chromium trioxide with pyridine have been used. Acetone, used as the reaction solvent, inhibits further oxidation of carbonyl-containing products and is, therefore, extremely useful. Various Cr(VI) oxidants have been employed in synthesis (see Ref. 10, pp. 221–234). Reagents prepared from chromic acid are efficient for the oxidation of isolated alcoholic groups in partially protected sugar derivatives. Pioneering work on Cr(VI) oxidations of sugar derivatives having free hydroxyl groups have been described in detail (Ref. 1, pp. 1139–1142). The properties of Cr(VI) and V(V) as oxidizing agents are also compared in Section XII.1.

The oxidizability of acetals was investigated by Angyal and James,¹³⁰ who found that acetylated methyl glycosides react with chromium trioxide–acetic acid to give acetylated methyl aldonates having a keto group in place of the oxygen atom formerly involved in the furanoid or pyranoid ring; methyl β -D-glucopyranoside tetraacetate (**46**) thus afforded methyl 2,3,4,6-tetra-*O*-acetyl-D-xylo-5-hexulose (47). Primary alkylidene acetals are opened to esters of ketoses by the same reagent¹³¹ 1,3,5,6-tetra-*O*-acetyl-2-*O*-benzylidene-D-glucitol (**48**) is thus oxidized to a *keto*-D-fructose derivative (**49**). Primary alkyl groups as aglycons¹³² or ether substituents¹³³ are similarly oxidized to acyloxy substituents (Scheme 22).

Oxidation of β -D-hexopyranosides by chromic acid is much faster than for their anomers,¹³⁰ and Hoffman *et al.*¹³⁴ have suggested the use of this reagent to cleave β -D-linkages selectively in heteropolysaccharides. The more-facile oxidation of the alcohol having the *endo* hydroxyl group was attributed to the relief of steric strain in the transition state as the trigonal carbonyl group is being formed, and to the unimolecular decomposition of the intermediate chromic ester through a cyclic transition-state that is

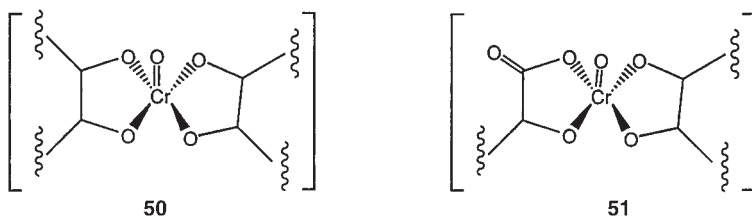


SCHEME 22

favored by the decrease in rotational freedom of the hindered ester. Steric factors may play an important role.¹³⁵ For example, 1-*O*-benzoyl-2,3:5,6-di-*O*-isopropylidenegalactitol undergoes ready oxidation at C-4 by chromic acid to afford the corresponding 3-hexulose derivative, whereas the stereoisomeric *manno*, *gulo*, and *allo* derivatives having a *cis* arrangement of the 1-*O*-benzoyl and 4-hydroxyl groups do not react with this reagent.

The chromic acid–pyridine complex oxidizes the free hydroxyl groups of carbohydrates to glycoloses. Horton *et al.*¹³⁶ reported good to fair yields for chromic acid–pyridine oxidations of a number of derivatives having an unprotected hydroxyl group in a primary or exocyclic secondary position, but endocyclic alcohol groups are generally less reactive. The basicity of pyridine can alter the stereochemistry of the product by epimerization of the carbon center α to the carbonyl group. Both pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) have been employed for the oxidation of sugar derivatives. For example, the 5-*O*-acylated derivatives of 1,4:3,6-dianhydro-D-glucitol and -D-mannitol gave the corresponding 2-keto derivatives in high yields.¹³⁷ Various reagents and procedures, including Swern oxidation, PDC, and tetra-*n*-propylammonium

tetraoxo-ruthenate(VII) with *N*-methylmorpholine *N*-oxide as cooxidant have been compared for the oxidation of aldose derivatives having the anomeric hydroxyl group free to the corresponding lactones.¹³⁸ The last of these reagents was very effective and afforded analytically pure lactones in 83–98% yield. The kinetics and synthetic aspects of the oxidation of sugars by PCC,¹³⁹ and the oxidation of aldoses and sugar phosphates by Cr(VI) have been reviewed.¹⁴⁰ Sala and co-workers studied the Cr(VI) oxidation of aldoses^{141–143} and deoxyaldoses^{141–145} in perchloric acid solution. For the 2-deoxy sugars, the lack of HO-2 accelerates the total reaction, and the HO-6 group may bind Cr(VI) as an intermediate ester. The kinetics of the reaction have been established by using an excess of sugar over Cr(VI). The redox reaction occurs through both Cr(VI) → Cr(III) and Cr(VI) → Cr(V) → Cr(III) pathways. Intermediate sugar alkoxide radicals may be trapped with 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and observed by electron paramagnetic resonance. These radicals react rapidly with Cr(VI) to form Cr(V). Such spectra showed that five- and six-coordinate oxochromate(V) intermediates are formed, with the aldose (**50**) or the aldonic acid (**51**) acting as bidentate ligands.¹⁴³ The oxidation of α - and β -D-glucose by Cr(VI) was conducted in dimethyl sulfoxide in the presence of pyridinium *p*-toluenesulfonate, a medium in which mutarotation is slower than the redox reaction. Both anomers reduce Cr(VI) by formation of an intermediate ester that is the precursor of the slow redox step. The equilibrium constant for the complex formation, and the rate of electron transfer within the complex, have been determined for each anomer. The equilibrium constant is higher for the α anomer, as the 1,2-*cis*-diolate moiety favors the Cr(VI) [or Cr(V)] chelation, and consequently, the activation barrier for the redox step is higher than that for the intermediate chelate formed from the β anomer. Because of the compensation of these two effects, the kinetic constants are of the same order for both anomers¹⁴⁶ (Scheme 23).



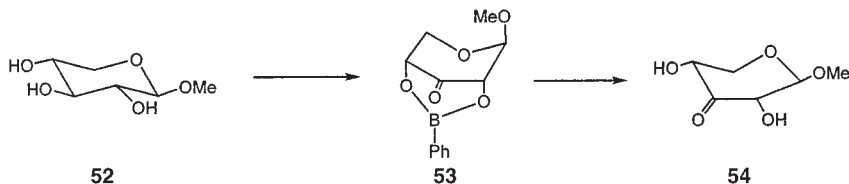
SCHEME 23

Investigation of a cellulose sample that had been oxidized by aqueous chromic acid in the presence of sulfuric acid showed that most

of the attack had occurred at C-3, as reduction and subsequent hydrolysis gave some D-allose, but no D-mannose.¹⁴⁷ The action of chromic acid on the 2-amino-2-deoxy analogue (chitosan) as the perchlorate (salt) was, however, directed almost exclusively to C-6 to afford an aminodeoxyglycopyranuronan.¹⁴⁸

IX. DIMETHYL SULFOXIDE

Pfitzner and Moffatt reported the use of methyl sulfoxide-*N,N'*-dicyclohexylcarbodiimide as an oxidizing reagent.¹⁴⁹ It was subsequently shown that anhydrides, and also a variety of reagents in combination with methyl sulfoxide, effect oxidation of isolated hydroxyl groups. This oxidation method in organic chemistry has been reviewed,¹⁵⁰ and Jones and co-workers¹⁵¹ presented a detailed comparison of the relative suitability of this and other oxidation methods for the oxidation of 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose to the corresponding 6-aldehyde derivative. Primary hydroxyl groups in partially protected sugar derivatives tend to react faster, but a number of side reactions have been reported. For example, partially acylated derivatives commonly undergo elimination of a molecule of acid to generate a site of unsaturation conjugated with the newly formed carbonyl group.^{152,153} Dimethyl sulfoxide-based oxidation of a number of sugar derivatives, and some side reactions that take place in individual cases, have been detailed in Ref. 1 (p. 1143). The Pfitzner-Moffat oxidation of isolated, secondary alcohol groups in otherwise protected molecules generally proceeds in good yield, whereas complicating side reactions are sometimes associated with similar reactions in the presence of more than one unprotected hydroxyl group. However, the difficulties that could be expected for the oxidation of unprotected methyl α - and β -D-xylopyranosides by this method are neatly avoided by the temporary introduction of a 2,4-cyclic phenylboronate protecting group prior to the oxidation; by this procedure, methyl β -D-xylopyranoside (**52**) was converted into methyl β -D-*erythro*-pentopyranosid-3-ulose (**54**) in 45% overall yield via the phenylboronate **53**¹⁵⁴ (Scheme 24). Successful



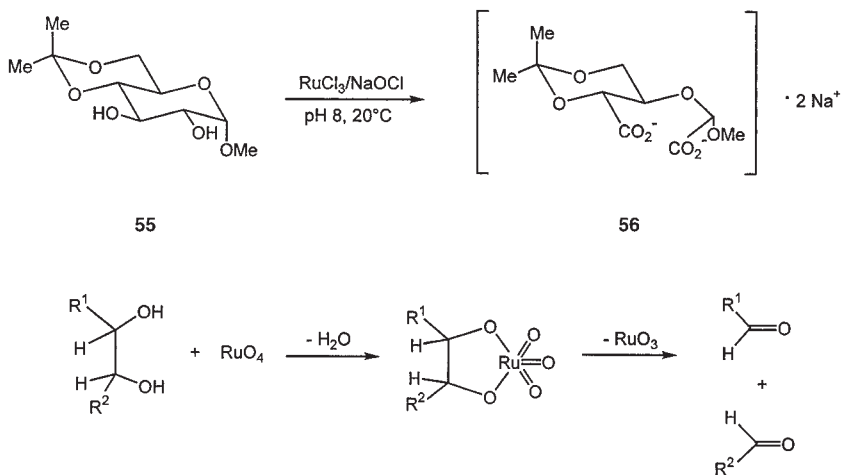
SCHEME 24

examples of selective oxidation of only one of several free hydroxyl groups of sugar derivatives and polysaccharides have been reported.¹

X. RUTHENIUM TETRAOXIDE

Ruthenium tetraoxide is a powerful oxidant; it is more reactive than osmium tetraoxide, and combines explosively with ether or benzene, so that it is generally used as a dilute solution in carbon tetrachloride. Beynon *et al.*¹⁵⁵ first demonstrated the usefulness of this reagent in carbohydrate chemistry by converting methyl 4,6-*O*-benzylidene-2-deoxy- α -D-ribo- and -D-arabino-hexopyranosides into methyl 4,6-*O*-benzylidene-2-deoxy- α -D-erythro-hexopyranosid-3-ulose.

The oxidant may be prepared before the reaction in the stoichiometric amount needed, or be generated *in situ* by reaction of a catalytic amount of ruthenium dioxide with periodate^{156,157} or hypochlorite.¹⁵⁸ Among a variety of oxidants studied, RuO₄ was found to be the best for the C-2–C-3 cleavage of methyl 4,6-*O*-isopropylidene- α -D-glucopyranoside (**55**) to the corresponding dicarboxylate **56**. In this case, RuO₄ was prepared *in situ* by oxidation of a catalytic amount of Ru(III) with sodium hypochlorite.¹⁵⁹ The presumed mechanism of the Ru-catalyzed diol cleavage is also shown in Scheme 25.



SCHEME 25

The catalytic method serves to minimize further oxidations, such as the Baeyer–Villiger reaction (see Section III); the latter reaction has been demonstrated to occur when the period of oxidation is extended.

The complex $\text{Ru}(\text{tpy})(\text{bpy})\text{O}_2^+$ [$\text{tpy} = 2,2',2''\text{-terpyridine}$, $\text{bpy} = 2,2'\text{-bipyridine}$] oxidizes organic substrates by hydride abstraction or oxo transfer. This complex, and its derivatives, cleave DNA by oxidation of the sugar at the 1' position and oxidation of guanine. Oxidation at the 1' position leads to the release of free bases and a furanone product. The kinetic parameters for the oxidation of D-ribose, "2-deoxy-D-ribose," and nucleotides by $\text{Ru}(\text{tpy})(\text{bpy})\text{O}_2^+$ were determined in phosphate buffer (pH 7). The increased reactivity of DNA as compared to RNA was rationalized on the basis of deactivation of the sugar oxidation product by the polar effect of the 2'-hydroxyl group.¹⁶⁰

Analytically pure lactones were obtained by oxidation of sugar derivatives, having the anomeric hydroxyl group free, with tetra-*n*-propylammonium tetraoxo-ruthenate(VII) and *N*-methylmorpholine *N*-oxide as cooxidant.¹³⁸

The use of ruthenium tetraoxide as an oxidant in organic chemistry has been reviewed¹⁶¹ and several applications to the carbohydrate field have been described (Ref. 1, p. 1147).

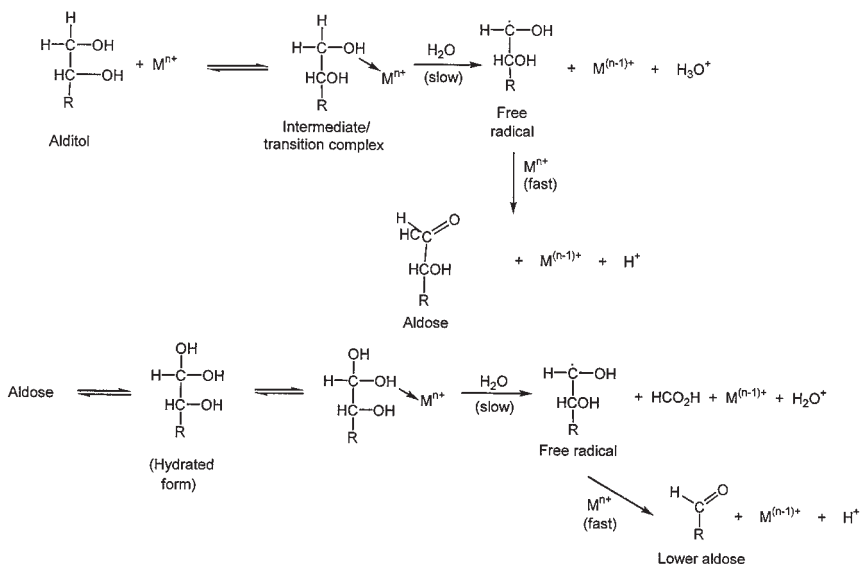
XI. PERMANGANATE AND MANGANESE OXIDES

Permanganate is a powerful oxidizing agent, but there are other oxidation states available to manganese, including manganate and hypomanganate. Their oxidizing power varies inversely with the charge of the oxidant.¹⁶² Primary and secondary alcohols are rapidly oxidized by alkaline permanganate; the reaction is slower in neutral and mildly acidic solutions. The rapid oxidation in alkaline solution has been attributed to the formation of a nucleophilic alkoxide anion. The choice of solvent is dictated by the type of protecting group used: acetates are oxidized in acetic acid, and isopropylidene acetals in alkaline solution. Unprotected glycol groupings and double bonds are usually attacked by alkaline permanganate, often resulting in carbon-carbon bond-cleavage. Under controlled conditions, permanganate (or osmium tetraoxide¹⁶³) effects *cis*-hydroxylation of double bonds. Examples of oxidation of a number of sugar derivatives by the action of permanganate have been given (Ref. 1, p. 1147).

The relative reactivities and kinetic behavior of some aldoses, amino sugars, and methylated sugars toward permanganate in perchloric acid medium have been studied.¹⁶⁴ The oxidation of the hemiacetal to the corresponding lactone is facile; in agreement, the oxidation of methyl glucopyranoside is much slower than that of the parent glucose. Kinetics have been also performed for the permanganate oxidation of pentoses, hexoses, and ketoses in aqueous alkaline media.¹⁶⁵

Manganese dioxide has been used to effect degradation of aldoses to the next lower aldoses.¹⁶⁶ Reducing disaccharides are converted into *O*-hexosylpentoses; further degradation to the *O*-hexosyltetrose is apparently obscured by oxidation of the tetrose residue to acidic products. Low yields of tetroses have been obtained from pentoses. Manganese dioxide has also been used for the oxidation of isolated alcohol groups of carbohydrates.¹

Manganese(III) has been employed for the oxidation of aldoses, and a general mechanism for the oxidation has been proposed.¹⁶⁷ The oxidation of hexoses, pentoses, hexitols, and pentitols by Mn(III), as well as by other cations, was proposed to proceed via a free-radical mechanism,¹⁶⁸ as shown in Scheme 26. Oxidation of alditols produces the corresponding aldoses, which are further oxidized in the presence of an excess of oxidant to the lower monosaccharides and thence to formaldehyde, formic acid, and even carbon dioxide. The kinetics for the oxidation of aldoses and ketoses by Mn(III) in sulfuric acid medium have been reported.¹⁶⁹



SCHEME 26

XII. MISCELLANEOUS OXIDANTS

1. Transition-Metal Cations

Oxidation of aldoses and ketoses with ferricyanide under alkaline conditions involves the 1,2-enediol as an intermediate. Such an oxidation

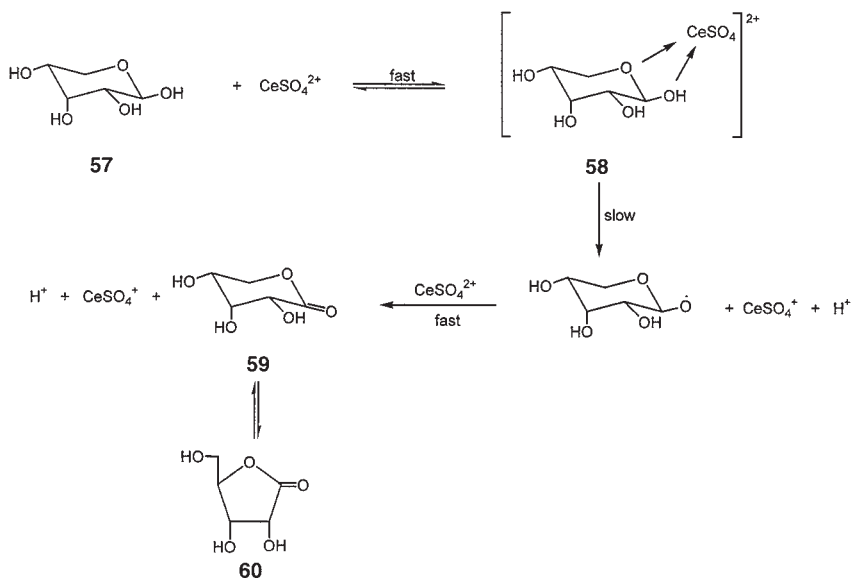
has been previously described in detail (Ref. 1, p. 1148). A number of studies on the kinetics of oxidation of sugars with transition-metal cations (vanadium, cerium, thallium, and others) have been conducted during the past two decades. Such studies are briefly summarized in this section. A review¹⁷⁰ has been published on the metal-ion oxidations of reducing sugars.

Polyhydroxy compounds are oxidized by such metal ions as vanadium(V), chromium(VI), cerium(IV), iridium(IV), and gold(III), among others. These oxidations were found to be catalyzed by acids.^{171–173} Vanadium(V) and chromium(VI) are closely related in their chemical properties, but the reduction of V(V) is difficult compared with that of Cr(VI) because of its lower redox potential [$V(V)$ – $V(IV)$ = 1.00 V; $Cr(VI)$ – $Cr(III)$ = 1.20 V]. However, the redox potential increases at lower pH values, facilitating the oxidation of sugars.

The hydroxyl groups of polyhydroxy compounds are readily esterified by vanadate, as demonstrated by ⁵¹V NMR.¹⁷⁴ The kinetics of oxidation of pentoses and hexoses,¹⁷² and D-erythrose and glyceraldehyde,¹⁷³ by vanadium(V) and chromium(VI) in perchloric acid was shown to be first order in oxidant and substrate. The reactions are catalyzed by acid, but their dependence on acidity is complex. The activation parameters were calculated and radical mechanisms, consistent with the experimental observations, were proposed. Thus, it was suggested that V(V) reacts with the hydrated aldoses to yield free-radical intermediates and VO^{2+} . The free radical is further oxidized by another $VO(OH)^{2+}$ cation in a fast step to give the products. The effect of pressure on the rates of oxidation of aldoses and ketoses by V(V) in perchloric acid has been investigated.¹⁷⁵ The negligible dependence in all of the cases on pressure up to 200 MPa was interpreted as demonstrating the formation of activated monosaccharide–vanadium complexes. It was suggested that, in the rate-determining decomposition of these complexes, hydrogen transfer takes place from the substrate to $V(OH)_2^{3+}$ to give a carbohydrate radical which undergoes rapid C–C or C–H bond fission. Oxidation is facilitated by a neighboring carbonyl group, which stabilizes the carbohydrate radical.¹⁷⁶ D-Fructose and L-sorbose give dicarbonyl compounds as primary products, and aldopentoses furnish aldotetroses. The reduction of V(V) and Mo(VI) in aqueous HCl by various hexoses, pentoses, ethylene glycol, and ethanolamine showed that the reducing abilities of these compounds are comparable with those of L-ascorbic acid and cysteine.¹⁷⁷

Spectrophotometric studies on the kinetics of oxidation of some aldoses by Ce(IV) in sulfuric acid medium show that, as similar with oxidations with V(V), the reactions are first order with respect to the cation and aldose concentration. The formation of a radical as the rate-determining step has been proposed.¹⁷⁸ In fact, the oxidation of hexoses,

pentoses, hexitols, and pentitols by V(V), Ce(IV), Mn(III), and Tl(III) in aqueous acidic media have been claimed to proceed by a radical mechanism.¹⁷⁹ It has been shown that cyclic pyranoid forms (such as **58**), and not the aldehydo forms, of D-glucose and D-ribose (**57**) are involved in their oxidation with metal ions. The lactones (**59** and **60**) are the initial products of oxidation (Scheme 27).

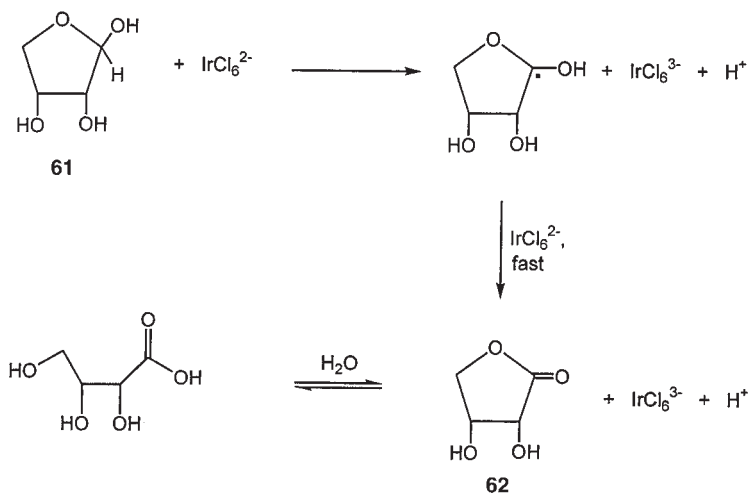


SCHEME 27

In perchloric acid, hexoses and pentoses are oxidized by Ce(IV) via formation of two complex intermediates. The first is partly oxidized following Michaelis–Menten kinetics and partly dissociated to the second, which is oxidized more slowly than the former.¹⁸⁰ The first step in the oxidation of aldoses by Tl(III) in the same medium involves the C-1–C-2 cleavage of the aldehydo form of the sugar. Thus, D-glucose gives D-arabinose and formic acid. With an excess of oxidant the final product is carbon dioxide.¹⁸¹ In the presence of a catalytic amount of sulfuric acid in acetic acid, Tl(III) oxidizes maltose and lactose to the corresponding disaccharide aldonic acids. The reaction showed activation enthalpies and entropies characteristic of second-order reactions.¹⁸²

Many other cations of transition metals have been employed for the oxidation of sugars. For example, the oxidation of aldoses by hexachloroiridate(IV)^{183,184} and tetrachloroaurate(III)^{183,185} in hydrochloric acid led to the corresponding aldonic acids or aldonolactones. The observed

reaction orders respective to cation and substrate suggested the formation of a free-radical intermediate by fission of the anomeric C–H bond. Such a radical is then converted into the products. The oxidation of D-erythrose (**61**) by hexachloroiridate(IV) is shown in Scheme 28. The oxidation of D-glucose 6-phosphate by these two complex species was also studied.¹⁸⁶



SCHEME 28

Most of the oxidations described in this section were performed in order to ascertain their mechanisms, but in general, they have not been employed for preparative purposes.

2. Copper(II) Oxide and Copper(II) Salts

The kinetics of oxidation by copper(II) in the presence of alkaline citrate and tartrate revealed that, as with ferricyanide, the rate of reaction is zero order in oxidant and directly proportional to the concentration of sugar and hydroxide ion; similar results were obtained for the oxidation of D-glucose with cupric ion complexed as the picolinate. The oxidation seems to proceed via a chelated cuprous complex of the enediol.¹ Methods for the quantitative determination of reducing sugars are based on oxidation with hot, alkaline solutions of copper salts (for example, the Soldaini and Fehling reagents). The oxidation products are, in general, monobasic acids having one to six carbon atoms, accompanied by oxalic acid, carbon dioxide, and lactic acid.

The kinetics of the Cu(II) oxidation of D-glucose¹⁸⁷ and D-galactose¹⁸⁸ under acidic conditions (pH 4–5 and 110 °C), and the kinetics of oxidation of L-ascorbic acid by Cu(II) at different pH values have been reported.¹⁸⁹

In ammoniacal solutions of copper salts, the oxidation products are likely to contain nitrogen; thus, hexoses give oxalic acid, imidazoles, hydrogen cyanide, and urea. Kinetic studies have been reported for the reaction of Cu(II) in the presence of ammonia with maltose, lactose, melibiose, and cellobiose.¹⁹⁰ For the oxidation by tetraamminecopper(II) in ammoniacal and buffered media the rate of reaction is first order in disaccharide concentration, order one-half in ammonia concentration, but it is independent of Cu(II) concentration. The reaction rate is decreased by the addition of ammonium chloride, because of the common ion effect. These kinetics suggested mechanisms involving an intermediate enediolate ion, with the rate of reaction being equal to the rate of enolization.¹⁹¹ A similar mechanism has been proposed for the oxidation of D-fructose by a copper–pyridine complex in an excess of pyridine.¹⁹²

3. Silver Oxide

The oxidation of carbohydrates by silver oxide at 50 °C (in water or potassium hydroxide) and the use of alkaline silver solutions for the detection of spots on paper chromatograms have been summarized in Ref. 1 (p. 1149). That review also describes common uses of the Fétizon reagent (silver carbonate suspended on Celite)¹⁹³ for oxidizing different types of sugar derivatives. Silver(II) picolinate has been employed as an oxidant for isolated hydroxyl groups;¹⁹⁴ with this reagent, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose was converted into the corresponding 1,4-lactone, and methyl 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranoside into the L-*lyxo*-hexofuransid-5-ulose derivative.

4. Sulfite Pulping

The sulfite process for delignification of wood in the paper industry involves heating with acidic sulfite solutions at elevated temperatures under pressure. Under such conditions, oxidation occurs to a certain extent, and presumably, the sulfite is partly reduced to sulfide. The composition of the liquors resulting from the treatment of cellulose and hemicelluloses, and alditols with sulfite in acid medium has been described (Ref. 1, p. 1150).

5. Wet Combustions

Oxidations of carbohydrates conducted under strongly acidic or strongly alkaline conditions are quite drastic, often completely degrading the substrate to carbon dioxide and water. Extremes of pH enhance either (a) the effectiveness of the oxidant by converting it into a stronger Lewis acid (at low pH), or (b) the nucleophilicity of the organic substrate by deprotonating it to an anion (or carbanion) (at high pH). The high electron density of the latter, negatively charged species facilitates the removal of either a hydride ion or a hydrogen atom, and expedites electron transfer to the oxidant.

The effects of such oxidants as a mixture of potassium iodate and dichromate in concentrated sulfuric and phosphoric acids (van Slyke reagent), hot solutions of chromic acid, and acidic solutions of ceric sulfate, permanganate, periodate, and hyperoxidized transition metals on a number of sugar derivatives has been described (Ref. 1, pp. 1151–1153).

XIII. ENZYMATIC AND MICROBIAL OXIDATIONS

Fermentative processes are of considerable value for the production of useful organic chemicals from carbohydrate precursors. Large amounts of acetic acid, acetone, butanol, citric acid, ethanol, D-gluconic acid, lactic acid, and L-sorbose are made industrially by fermentation. In fermentative processes, oxidizing as well as reducing conditions may be employed, depending on the product desired. Laboratory and industrial preparation of many other substances, such as glycols, have been carried out by using enzymes.

Microorganisms exhibit a marked specificity in their choice of substrates, and in the reaction products. This property is useful for the qualitative and quantitative determination of sugars, as well as for the identification of microorganisms. The formation of glycuronic, aldonic, and glycosonic acids, and glycosuloses is considered in the preceding Chapter and the bacterial oxidations of aldoses to 2- or 5-hexulosonic, or 2,5-dihexulosonic acids, as well as the formation of hexulose derivatives, have been described in detail (Ref. 1, pp. 1153–1156). Enzymatic approaches to the synthesis of mono- and oligosaccharides and related structures, including those involved in carbohydrate recognition,¹⁹⁵ as well as the oxidations of polyols to polyhydroxyaldehydes by enzymes, and the useful applications of enzymatic oxido-reductions in organic synthesis¹⁹⁶ have been reviewed.

Alditols are oxidized by certain microorganisms; for example, *Acetobacter suboxydans* converts D-mannitol into D-fructose; the oxidation may occur

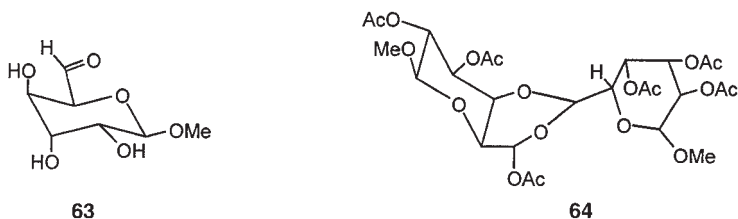
on either C-2 or C-5 because the two atoms are related by symmetry. Isbell *et al.*¹⁹⁷ used isotopically labeled D-mannitol to prove that dissociation of the carbon–hydrogen bond at C-2 (or C-5) is the rate-determining step.

The enzyme glucose oxidase (EC 1.1.3.4), also called *notatin*, catalyzes the oxidation of D-glucose by molecular oxygen to D-gluconic acid. It has been isolated from various molds, especially *Aspergillus niger* and *Penicillium glaucum*. The enzyme is highly specific for β -D-glucopyranose.¹⁹⁸ As the initial reaction product is D-glucono-1,5-lactone, the pyranose ring remains intact, as with bromine oxidation; hydrogen peroxide is also formed.

Glucose oxidase was initially considered to act as an oxidase, but experiments with ordinary molecular oxygen and water enriched with ^{18}O showed that the action is that of a dehydrogenase, which catalyzes the transfer of two hydrogen atoms from D-glucose to gaseous oxygen.¹⁹⁹ The enzyme is commonly used for determining D-glucose, and it has been used in a method for determining the aeration capacity of fermentation tanks.²⁰⁰ It has also found use in application as a glucose sensor in diabetes control.²⁰¹

A purified D-glucose dehydrogenase, isolated from animal liver, catalyzes the oxidation of D-glucose to D-gluconic acid.²⁰² A coenzyme (either nicotinamide adenine dinucleotide or its 2'-phosphate) is necessary for the oxidation. The reaction is reversible, and is specific for β -D-glucopyranose; it does not proceed with the α -D anomer, and it occurs only slowly with D-xylose.

D-Galactose oxidase (EC 1.1.3.9) removes the *pro-S* hydrogen atom²⁰³ from C-6 of D-galactopyranose derivatives to produce initially the D-*galacto*-hexodialdo-1,5-pyranose analogues.²⁰⁴ Thus, in the case of methyl β -D-galactopyranoside, the hexodialdo-1,5-pyranose (**63**) has been characterized, after acetylation, in a dimeric form (**64**). Simultaneously, O_2 is reduced to H_2O_2 , which in the presence of the enzyme catalase is decomposed to H_2O and O_2 . D-Galactose oxidase is produced by numerous species of fungi, but it is commonly obtained from *Dactylium dendroides*. The kinetic solvent isotope effect of the enzyme isolated from this microorganism suggests that one electron of O_2 is transferred to a transition state that is stabilized by a hydrogen bond from water bound to Cu(II) in the active site²⁰⁵ (Scheme 29).

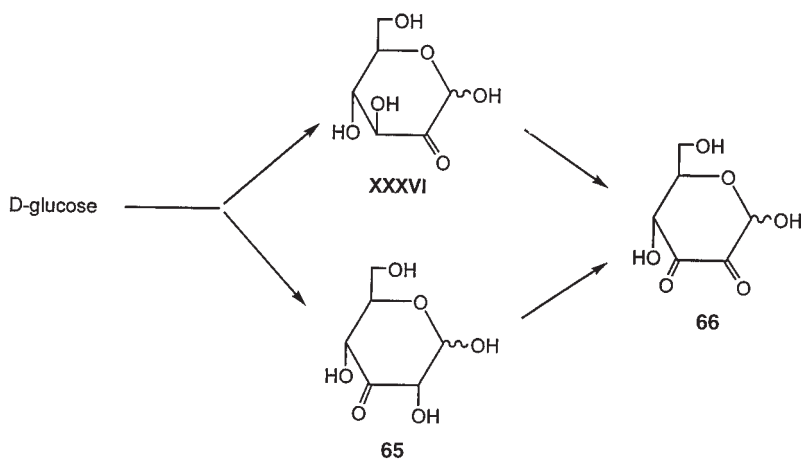


SCHEME 29

Galactose oxidase is specific for D-galactose, but it also oxidizes some simple derivatives and various oligosaccharides containing galactose at the nonreducing end. Alditols have been successfully oxidized to the corresponding sugar by galactose oxidase.²⁰⁶ The oxidation of D-[6-³H]galactose by this enzyme showed a large kinetic isotope effect. As the unlabeled substrate is oxidized faster, material enriched in the labeled component was obtained upon incomplete oxidation of partially labeled starting galactose.²⁰⁷

Rogers and Thompson²⁰⁸ used the action of this enzyme, and subsequent oxidation by bromine, to effect the conversion of a galactomannan into a galacturonomannan; a similar sequence has been used with glycoproteins as a method for linkage analysis.²⁰⁹

Characteristic for wood-degrading fungi seems to be the growing family of pyranose 2-oxidases (glucose-2-oxidases, EC 1.1.3.10), enzymes that act as a C-2 specific oxidase of several aldopyranoses,²¹⁰ with D-glucose being the favored substrate. The product of oxidation is the dicarbonyl monosaccharide D-*arabino*-hexos-2-ulose, which plays an important role in sugar metabolism of numerous wood-degrading basidiomycetes, such as *Oudemansiella mucida*.²¹¹ Also, the quinone-dependent sugar oxidoreductase, pyranose dehydrogenase purified from *Agaricus bisporus* catalyzed the C-2 or C-3 oxidation of D-glucose to D-*arabino*-hexos-2-ulose (**36**) and, preferentially, D-*ribo*-hexos-3-ulose (**65**). The two aldoketoses accumulate transiently and are finally converted into the same end-product, D-*erythro*-hexose-2,3-diulose (**66**).²¹² D-Galactose is exclusively oxidized at C-2 to produce D-*lyxo*-hexos-2-ulose (Scheme 30).



SCHEME 30

Incubation of D-xylose with an aqueous solution of bovine lens protein gave both xylitol and xylonic acid. Studies of the reaction under a variety of conditions suggest that both the reduction and oxidation reactions are protein (possibly enzyme) catalyzed and appear to be unique to lens protein.²¹³

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5,7-DIAMINO-3,5,7,9-TETRADEOXYNON-2-ULOSONIC ACIDS IN BACTERIAL GLYCOPOLYMERS: CHEMISTRY AND BIOCHEMISTRY

BY YURIY A. KNIREL,^a ALEXANDER S. SHASHKOV,^a YURY E. TSVETKOV,^a
PER-ERIK JANSSON,^b AND ULRICH ZÄHRINGER^c

^aN. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia; ^bKarolinska Institute, Clinical Research Center, Huddinge University Hospital, Huddinge, Sweden; and ^cResearch Center Borstel, Center for Medicine and Biosciences, Borstel, Germany

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I. INTRODUCTION

Ald-2-ulosonic acids are important components of natural glycoconjugates. Sialic acids, namely *N*- and *O*-acyl derivatives of 5-amino-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (neuraminic acid, Neu), generally occur in glycoconjugates of vertebrates and play a significant role in recognition, regulation, and protection.^{1,2} A deamino analogue of neuraminic acid, 3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (Kdn),

has also been found in a variety of animal tissues.³ 3-Deoxy-D-manno-oct-2-ulosonic acid (Kdo) is an essential component of lipopolysaccharides (LPSs) of Gram-negative bacteria that functions to link the carbohydrate portion to the lipid moiety.^{4,5} In rare cases, Kdo in LPS is replaced with a 3-hydroxylated analogue, D-glycero-D-talo-oct-2-ulosonic acid.^{5,6} Neu, Kdn, Kdo, hex-2-ulosonic, 3- and 4-deoxyhex-2-ulosonic, and 3-deoxyhept-2-ulosaric acids have been identified in several bacterial polysaccharides.⁶⁻⁸

A new class of ald-2-ulosonic acids, 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids, reported as “sialic acids of a new type,” was discovered in 1984.⁹ Members of this class contain an additional amino group at C-7, additional deoxygenation at C-9 (methyl group) and may exhibit configurational differences as compared with neuraminic acid. Unlike sialic acids, the new class of ald-2-ulosonic acids appears to be unique to microorganisms.

A short review article¹⁰ in 1987 highlighted the occurrence and chemical properties of two isomers of 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids. Since that time, the configuration of one of these sugars was revised and new isomers have been discovered.^{11,12} Sugars of this class have been reported as components of a variety of bacterial LPSs as well as several capsular polysaccharides (CPSs)^{13,14} and glycoproteins.^{15,16} Further, various isomers have been synthesized and NMR spectroscopic data accumulated for identification of such sugars.^{11,17,18}

The present article focuses on the occurrence and characterization of derivatives of 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids and presents experimental approaches used to identify them and to elucidate the structures of the bacterial polysaccharides that contain the nonulosonic acids. Recent data on the biosynthesis of these sugars and their role in immune recognition and epitope specificity of bacterial glycopolymers are discussed.

II. NATURAL OCCURRENCE, BIOSYNTHESIS, AND BIOLOGICAL SIGNIFICANCE

1. Occurrence and Structural Features of the Natural Sugars

The first 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acid was discovered simultaneously in the O-chain polysaccharides (OPSs) of LPSs of *Pseudomonas aeruginosa* O7 and O9¹⁹ and *Shigella boydii* type 7 (for a review see Ref. 10). The nonulosonic acid was identified as the L-glycero-L-manno isomer (**1**) and called pseudaminic acid.²⁰⁻²⁴ Later, pseudaminic acid was found in LPSs of several other Gram-negative bacteria²⁵⁻²⁹

TABLE I
Occurrence of Derivatives of 5,7-Diamino-3,5,7,9-tetradexynon-2-ulosonic Acids (1–4) in
Bacterial Polysaccharides

N-Acyl Substituents ^a		Bacterial Source ¹⁹	References
at N-5	at N-7		
L-glycero-L-manno isomer (pseudaminic acid, Pse, 1)			
Ac	Ac	<i>Escherichia coli</i> O136	26
Ac	Ac	<i>Proteus vulgaris</i> O39	28
Ac	Ac	<i>Pseudoalteromonas atlantica</i> T9	29
Ac	Fo	<i>Pseudomonas aeruginosa</i> O7a,7b,7d and O7a,7d (immunotype 6)	21,23
		<i>Pseudoalteromonas distincta</i> KMM 638	27
R3Hb	Fo	<i>Pseudomonas aeruginosa</i> O7a,7b,7c	23
Ac	R3Hb	<i>Pseudomonas aeruginosa</i> and O9a,9b	20,22
		<i>Shigella boydii</i> type 7	20,24
		<i>Sinorhizobium fredii</i> HH103	14
Ac	S3Hb	<i>Sinorhizobium fredii</i> HH103	14
Am	Ac	<i>Vibrio cholerae</i> O:2	25
D-glycero-D-galacto isomer (legionaminic acid, Leg, 2)			
Ac	Ac	<i>Vibrio alginolyticus</i> 945-80	11,33
		<i>Acinetobacter baumannii</i> O24	11,35
S3Hb	Ac	<i>Acinetobacter baumannii</i> O24	11,35
Am	Ac	<i>Legionella pneumophila</i> serogroup 1	11,31
		<i>Pseudomonas fluorescens</i> ATCC 49271	11,32
		<i>Vibrio salmonicida</i> NCMB 2262	11,34
L-glycero-D-galacto isomer (8-epilegionaminic acid, 8eLeg, 3)			
Ac	Ac	<i>Pseudomonas aeruginosa</i> O12	22
4Hb	Ac	<i>Yersinia ruckeri</i> O1	36
R3Hb	Ac	<i>Salmonella arizonae</i> O61	37
Am	Ac	<i>Morganella morganii</i> KF 1676 (RK 4222)	38
Ac	Am	<i>Shewanella putrefaciens</i> A6	39
D-glycero-D-talo isomer (4-epilegionaminic acid, 4eLeg, 4)			
Ac	Ac	<i>Legionella pneumophila</i> serogroup 1	11,12
Am	Ac	<i>Legionella pneumophila</i> serogroup 2	40

^aAm, acetimidoyl; Fo, formyl; R3Hb and S3Hb, (R)- and (S)-3-hydroxybutanoyl; 4Hb, 4-hydroxybutanoyl.

(Table I) and CPSs of *Sinorhizobium*.^{13,14} Recently, pseudaminic acid or its enantiomer has been reported as a component of surface bacterial glycoproteins: pilin of *P. aeruginosa*¹⁵ and flagellins of *Campylobacter jejuni* and *Campylobacter coli*.¹⁶

In 1987, a second isomer of this class was found in OPS of *P. aeruginosa* O12 and thought to have the D-glycero-L-galacto configuration.³⁰ The same, or mistakenly inferred as the same, sugar was reported to be present in a

number of other bacterial polysaccharides,^{31–37} including LPS of *Legionella pneumophila* serogroup 1,³¹ and was named legionaminic acid. In 1996, the configuration of legionaminic acid was revised to the opposite configuration.^{32,34} Using synthetic models (Section III.1), it was finally determined that two isomers differing in the configuration at C-8 exist in different bacterial polysaccharides.¹¹ The D-glycero-D-galacto isomer (**2**) that has the same configuration as neuraminic acid kept the name legionaminic acid. It was present in *L. pneumophila*³¹ and several other bacteria^{32–35} (Table I). The other, L-glycero-D-galacto isomer (**3**) found in *P. aeruginosa* O12³⁰ and four more bacteria^{36–39} (Table I) was called 8-epilegionaminic acid. The data that prompted the aforementioned revisions have been summarized.¹¹

A fourth sugar was found only in LPS of *L. pneumophila*.^{12,40} It was initially identified as the L-glycero-D-talo isomer¹² but later revised to the D-glycero-D-talo isomer and named 4-epilegionaminic acid (**4**).^{11,40} Two more stereoisomers of the nonulosonic acids were found in several other *L. pneumophila* isolates⁴⁰ but their configurations have not yet been determined.

The naturally occurring isomers **1–4** have the same configuration at C-6, whereas the configurations of the other chiral centers may be different (Fig. 1). In aqueous solution, the free sugars exist in the ²C₅ pyranose form as mixtures of α and β anomers with a predominance of the thermodynamically more stable anomer having an equatorial carboxyl group. According to the Nomenclature of Carbohydrates,⁴¹ the reference atom for the definition of the anomeric configuration is the highest-numbered atom of the group of chiral centers next to the anomeric center that is specified by a single configurational prefix. For 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids the reference atom is C-7, which has the L configuration in pseudaminic acid **1** and the D configuration in legionaminic acid **2** and the epimers **3** and **4**. Correspondingly, Fig. 1 shows the α anomer of **1** and β anomers of **2–4**. In natural glycopolymers, pseudaminic and legionaminic acids may be α -linked or β -linked, and the anomers with an axial carboxyl group occur more frequently; 4- and 8-epilegionaminic acids are known only as α -glycosides.

Only N-acylated 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids are found in Nature. Although N-acetyl groups predominate, other substituents, such as formyl, (R)- and (S)-3-hydroxybutanoyl, 4-hydroxybutanoyl, and acetimidoyl groups, are not uncommon. N-Acetyl and N-acetimidoyl groups are found in all known natural isomers, whereas other N-acyl groups are restricted to one or two isomers (Table I). Sometimes the nonulosonic acids are O-acetylated at position 4^{22,24} or 8,^{12,31,32,40} 8-O-acetylation being nonstoichiometric in *Pseudomonas fluorescens*³² and some *L. pneumophila* serogroups.⁴⁰

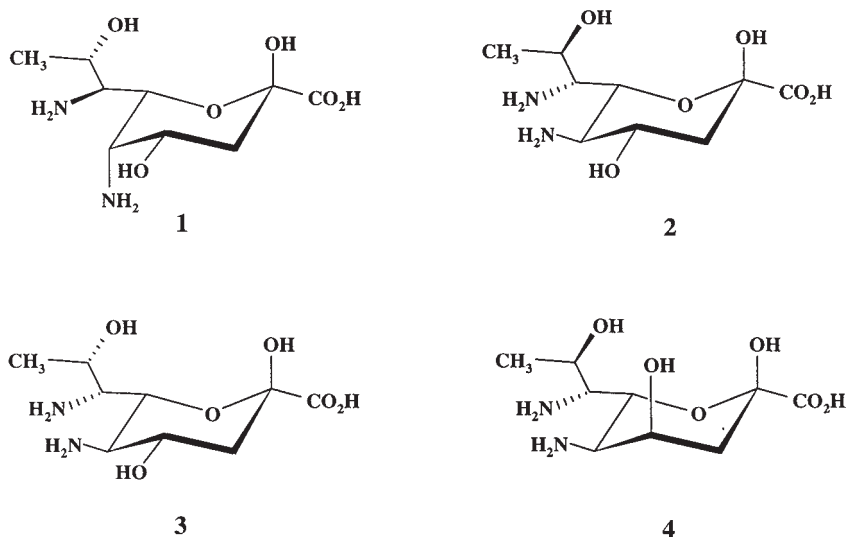


FIG. 1. Naturally occurring isomers of 5,7-diamino-3,5,7,9-tetradexonon-2-ulosonic acids 1–4. [Shown are thermodynamically more stable anomers with an equatorial carboxyl group, which correspond to the α anomer of 1 (L-glycero-L-manno isomer, pseudaminic acid, Pse) and the β anomer of 2 (D-glycero-D-galacto isomer, legionaminic acid, Leg), 3 (L-glycero-D-galacto isomer, 8-epilegionaminic acid, 8eLeg), and 4 (D-glycero-D-talo isomer, 4-epilegionaminic acid, 4eLeg).]

2. Structures of Bacterial Glycopolymers

The known polysaccharides containing 5,7-diamino-3,5,7,9-tetradexonon-2-ulosonic acids are diverse. They vary from homopolymers^{14,31,32,40} to heteropolysaccharides that contain pentasaccharide repeating units.^{12,29} Homopolysaccharides are known for all naturally occurring isomers except 8-epilegionaminic acid. Pseudaminic, legionaminic, and 8-epilegionaminic acids, but not 4-epilegionaminic acid, have been reported as constituents of heteropolysaccharides.

a. Pseudaminic Acid.—The CPS of *Sinorhizobium fredii* HH103 (5) is a homopolymer of 5-*N*-acetyl-7-*N*-(3-hydroxybutanoyl)- α -pseudaminic acid, the 3-hydroxybutanoyl group being present as a 3:1 mixture of the *R* and *S* isomers¹⁴ (Fig. 2). This polysaccharide is unusual because the sugar residues are linked through a glycosidic linkage to the hydroxyl group of the *N*-(3-hydroxybutanoyl) group, and thus represents a copolymer of pseudaminic acid and 3-hydroxybutanoic acid.

OPs of *P. aeruginosa* O9 (6, 7) include the same pseudaminic acid derivative but with the (*R*)-3-hydroxybutyryl group at N-5²² (Fig. 2).

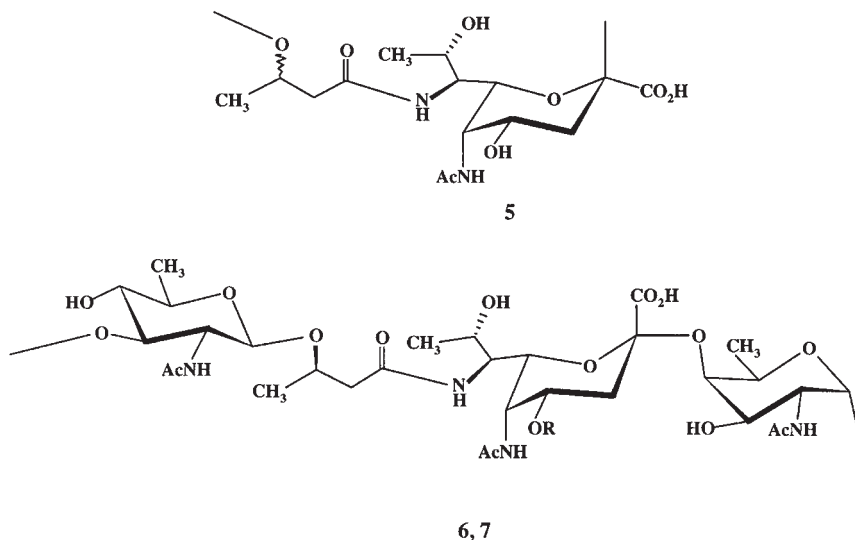


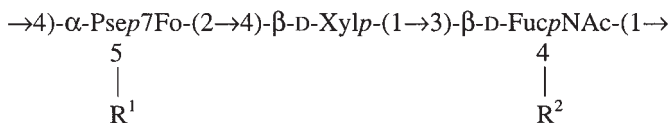
FIG. 2. Structures of CPS of *Sinorhizobium fredii* HH103 (**5**)¹⁴ and OPSs of *Pseudomonas aeruginosa* O9 (**6,7**)²² [6 R = H (subgroup O9a), 7 R = Ac (subgroup O9a,9b)].

The repeating units are connected by both glycosidic and amidic bonds through the *N*-(3-hydroxybutanoyl) group, namely by the same linkage as occurs in the polysaccharide of *S. fredii*.¹⁴ Two other components of the trisaccharide repeating units are 2-acetamido-2,6-dideoxy-D-glucose (D-QuiNAc) and 2-acetamido-2,6-dideoxy-D-galactose (D-FucNAc). Position 4 of pseudaminic acid is *O*-acetylated in serogroup O9a,9b but not in serogroup O9a (Fig. 2).

OPSs of *P. aeruginosa* serogroup O7 (**8–10**) include a derivative with a formyl group at N-7 and either an acetyl or (*R*)-3-hydroxybutanoyl group at N-5.²³ This variability, along with the presence or absence of the *O*-acetyl group at O-4 of the neighboring D-FucNAc residue, is the basis for subdivision of the O7 serogroup into three subgroups (Fig. 3).

Pilin of *P. aeruginosa* strain 1244, a ~16 kDa glycoprotein of the somatic pili, contains an O-linked pseudaminic acid-containing trisaccharide (**11**) attached to a serine residue in each pilin monomer (Fig. 3).¹⁵ The trisaccharide has the same structure as the repeating unit of OPS of *P. aeruginosa* O7a,7b,7c except for the absence of the *O*-acetyl group in the D-FucNAc residue. Further studies should show if the OPS repeating unit of *P. aeruginosa* 1244 has the same structure as that of *P. aeruginosa* O7a,7b,7c and, thus, as the pilin trisaccharide.

Single O-linked residues of pseudaminic acid derivatives (or its enantiomer) modify flagellin, the major structural protein of the



8 $\text{R}^1 = (R)\text{-3-hydroxybutanoyl}$, $\text{R}^2 = \text{Ac}$ (subgroup O7a,7b,7c)

9 $\text{R}^1 = \text{R}^2 = \text{Ac}$ (subgroup O7a,7b,7d)

10 $\text{R}^1 = \text{Ac}$, $\text{R}^2 = \text{H}$ (subgroup O7a,7d or immunotype 6)

$\alpha\text{-Psep5(3Hb)7Fo}-(2\rightarrow 4)-\beta\text{-D-Xylp}-(1\rightarrow 3)-\beta\text{-D-FucpNAc}-(1\rightarrow \text{O})\text{-Ser}$ 11

FIG. 3. Structures of OPSs of *Pseudomonas aeruginosa* O7 (**8–10**)²³ and the serine-linked trisaccharide chain of pilin of *P. aeruginosa* 1244 (**11**).¹⁵ (Pse, pseudaminic acid; FucNAc, 2-acetamido-2,6-dideoxygalactose.)

flagellar filament of *Campylobacter jejuni* and *Campylobacter coli*.¹⁶ In the ~65 kDa glycoprotein of *C. jejuni* 81-176, 19 of the total 107 Ser/Thr residues are glycosylated, and, hence, this is one of the most extensively modified prokaryotic proteins identified to date. Together with 5,7-di-*N*-acetyl-pseudaminic acid, 5,7-di-*N*-acetyl-8-*O*-acetyl, 5-*N*-acetimidoyl-7-*N*-acetyl, and 5,7-di-*N*-glyceroyl derivatives were tentatively identified. The anomeric configuration of the nonulosonic acid has not been assigned.

Structures of pseudaminic acid-containing OPSs from other bacteria (**12–16**) are shown in Fig. 4. OPSs of *Vibrio cholerae* O:2²⁵ (**13**) and *Escherichia coli* O136²⁶ (**14**) show marked structural similarities.

5,7-Di-*N*-acetyl-pseudaminic acid was also found in OPS of *Pseudoalteromonas atlantica* T9²⁹ and CPS of *Sinorhizobium* sp. NGR 234,¹³ and 7-*N*-acetyl-5-*N*-(3-hydroxybutanoyl)-pseudaminic acid in CPS of *Sinorhizobium meliloti* AK631.¹³ The data reported on the monosaccharides in the *Sinorhizobium* CPS are limited, and the full structure of none of the three polysaccharides has been determined.

b. Legionaminic Acid.—OPSs of all *L. pneumophila* serogroups are α (2→4)-linked homopolymers of 5-acetimidoylamino-7-acetamido-3,5,7,9-tetradexynon-2-ulosonic acids^{31,40} (structures **17** and **18** in Fig. 5). In serogroup 1, OPS is polylegionaminic acid, which is 8-*O*-acetylated in some strains³¹ (structure **17**) and mostly non-*O*-acetylated in the others.^{42,43} Accordingly, using mAbs that recognize 8-*O*-acetyllegionaminic acid (see Section II.4), serogroup 1 strains were divided into the Pontiac group and

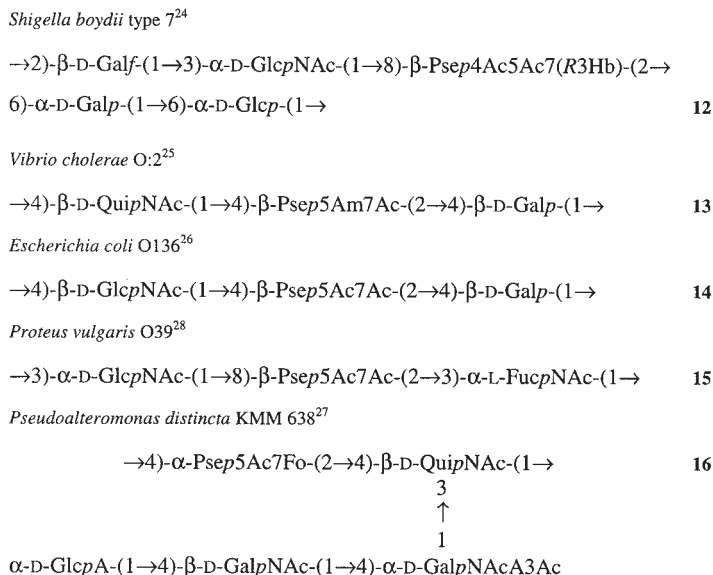


FIG. 4. Structures of OPSs containing pseudaminic acid (Pse). (QuiNAc, 2-acetamido-2,6-dideoxyglucose.)

the non-Pontiac group. The first three legionaminic acid residues next to the core in short-chain OPS (< 10 legionaminic acid residues) are 8-*O*-acetylated in both groups.⁴²

Derivatives of legionaminic acid that are mono- or di-*N*-methylated at the 5-*N*-acetimidoyl group (**19** and **20**) are minor components of LPS of *L. pneumophila* serogroup 1⁴⁴ (Fig. 5). The monomethyl derivative **19** occurs as two stereoisomers, *E* and *Z*, whereas only one isomer was observed for the dimethyl derivative **20**. Molecular modeling data suggested that this is the sterically less-hindered *E* isomer.⁴⁴ The *N*-methylated derivatives are present in LPS from both Pontiac and non-Pontiac groups and can be 8-*O*-acetylated in the Pontiac group. A single residue of **19** and **20** is located exclusively in long-chain OPS (> 10 legionaminic acid residues), most likely, close to the LPS core. *N*-Methylation is rare in bacterial polysaccharides,⁶ and no *N*-methylated acetimidoylamino (acetamidino) group has been found in other naturally occurring monosaccharides.

OPS of *P. fluorescens* has the same structure **17** as that of *L. pneumophila* serogroup 1 strain Philadelphia 1^{11,31} but the degree of *O*-acetylation is lower (~75%).³² *P. fluorescens* also produces an LPS with one monomer of the *O*-chain attached to the core oligosaccharide^{32,45} (structure **21** in Fig. 6). 5-*N*-Acetimidoyl-7-*N*-acetyllegionaminic acid was also found in the

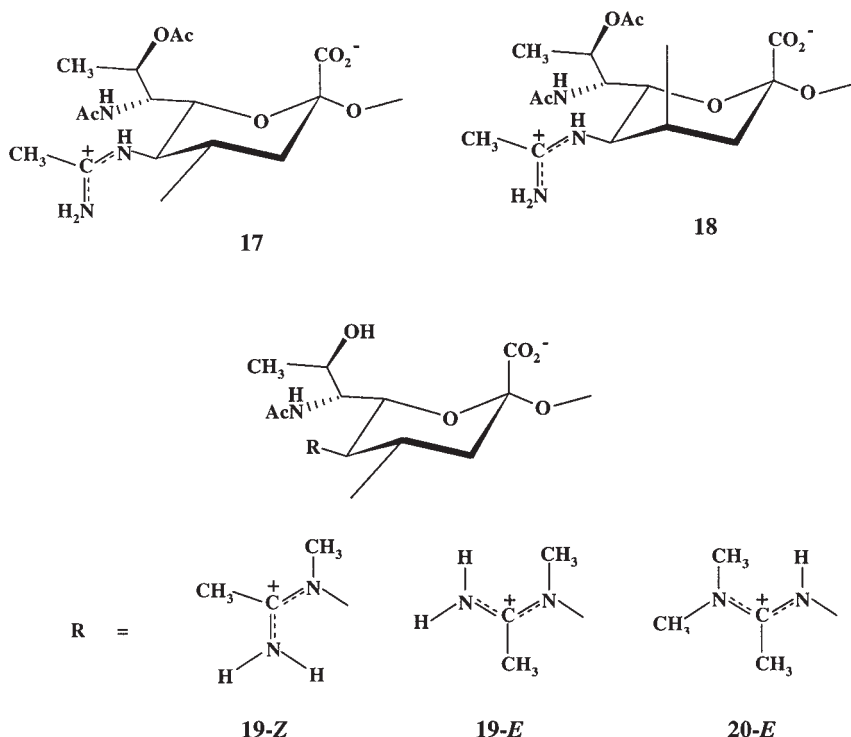


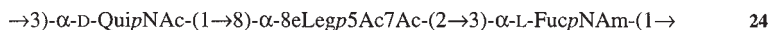
FIG. 5. Structures of OPS of *Legionella pneumophila* serogroup 1 strain Philadelphia 1 (17)^{11,31} and serogroup 2 (18)⁴⁰ and of the minor components of OPS of serogroup 1 (19 and 20).⁴⁴

oligosaccharide portion of short-chain LPS produced by *Vibrio salmonicida* (structure **22** in Fig. 6).

OPS of *Acinetobacter baumannii* O24 (**23**) is a heteropolysaccharide that contains a 5-*N*-acetyl derivative of legionaminic acid in about half of its tetrasaccharide repeating units and a 5-*N*-[(*S*)-3-hydroxybutanoyl] derivative in the remaining units³⁵ (Fig. 6).

5,7-Di-*N*-acetyllegionaminic acid was found in OPS of *Vibrio alginolyticus*,^{11,33} whose structure remains unknown. Short-chain LPSs of *Vibrio parahaemolyticus* O2 and KX-V212 (O-untypable strain) contain 5,7-di-*N*-acetyl and 5-*N*-acetyl-7-*N*-(*N*-acetyl-L-alanyl) derivatives of legionaminic acid, respectively.⁴⁶ The former was suggested to be involved in defining the serological specificity of the bacterium.⁴⁶

c. 8-Epilegionaminic Acid.—Polysaccharides containing 8-epilegionaminic acid can be divided into two structural groups. One group that contains

Pseudomonas aeruginosa O12³⁰*Yersinia ruckeri* O1³⁶

3

↑

1

 $\beta\text{-D-GlcpNAc}$ *Salmonella arizonae* O61³⁷

FIG. 7. Structures of OPSs containing 8-epilegionaminic acid (8eLeg).

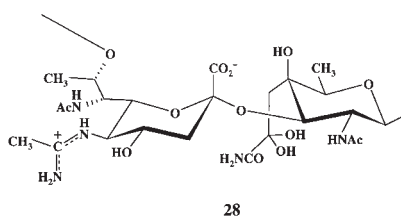
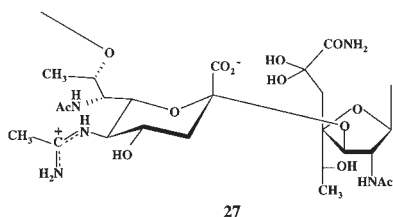
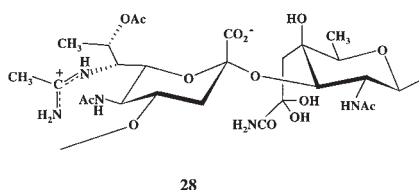
Morganella morganii KF 1676³⁸*Shewanella putrefaciens* A6³⁹

FIG. 8. Structures of OPSs containing 8-epilegionaminic acid and shewanellose.

position, the location of N-linked substituents (acetyl and acetimidoyl groups) and the presence or absence of an *O*-acetyl group in 8-epilegionaminic acid.

d. 4-Epilegionaminic Acid and Unidentified Isomers.—OPS of *L. pneumophila* serogroup 2 is an 8-*O*-acetylated homopolymer of 5-*N*-acetimidoyl-7-*N*-acetyl-4-epilegionaminic acid⁴⁰ (**18**) (Fig. 5). In most other serogroups except serogroups 7 and 13 and some strains of serogroup 5,

OPS is the same homopolysaccharide that is 8-*O*-acetylated to varying degrees (from <10 to >90%).⁴⁰ In OPSs of serogroups 5 and 13, 4-epilegionaminic acid is a minor constituent, whereas the major is an unidentified isomer. OPS of serogroup 7 is composed of yet another isomer, whose configuration also remains to be determined.

5,7-Di-*N*-acetyl-4-epilegionaminic acid is present in LPS of *L. pneumophila* serogroup 1^{11,12} but the site of attachment of this sugar to LPS has not been determined.

3. Biosynthesis

In contradistinction to sialic acids,^{1,2} little is known about biosynthesis of 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids. Some data are available on biosynthesis of derivatives of pseudaminic acid¹⁶ and legionaminic acid⁴⁷ in human pathogens *C. jejuni* and *L. pneumophila*.

a. Pseudaminic Acid.—Genomic sequencing of *C. jejuni* NCTC 11168 revealed the presence of multiple alleles of genes encoding proteins predicted to be involved in Neu5Ac biosynthesis.⁴⁸ Whilst one set comprises genes of biosynthesis of Neu5Ac found in the LPS core of *C. jejuni*, the other two sets are involved in modifications of flagellin, a protein glycosylated with single residues of di-*N*-acetylpsseudaminic acid and several other derivatives, including 5-*N*-acetimidoyl-7-*N*-acetylpsseudaminic acid¹⁶ (Section II.2). Mutations in genes termed *ptmB* and *neuB3* encoding a putative acylneuraminate cytidyl transferase (CMP-Neu5Ac synthase) and a putative Neu5Ac synthase, respectively, affected flagellin (Ref. 16 and references cited therein). The *neuB2* and *neuB3* gene products showed homology to NeuB, *E. coli* K1 Neu5Ac synthase that catalyzes condensation of mannosamine and enolpyruvate phosphate to form sialic acid. Therefore, the enzyme encoded by either of the *neuB* genes might be involved in the condensation of a C₆ precursor (e.g., a 2,4-diacetamido-2,4,6-trideoxyhexose) and a C₃ precursor (an activated pyruvate form) to give Pse5Ac7Ac in a similar fashion.

In the genome region of *C. jejuni* 81-176, open reading frame (ORF) Cj1316c encoding a predicted protein of 43.7 kDa is located adjacent to ORF Cj1317 corresponding to the *neuB3* gene. The ORF Cj1316c gene termed *pseA* was suggested to be involved in biosynthesis of the acetamidino group on pseudaminic acid.¹⁶ While insertional inactivation of *neuB3* caused loss of motility, mutation of *pseA* resulted in a motile phenotype. Flagellin from the *pseA* mutant no longer contained *N*-acetimidoyl groups, all Pse5Am7Ac residues present in the wild-type flagellin being replaced by Pse5Ac7Ac residues. The *pseA* gene product shares significant similarity

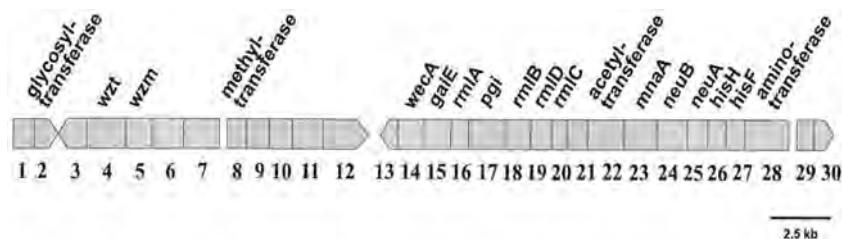


FIG. 9. Lipopolysaccharide biosynthesis locus of *Legionella pneumophila* serogroup 1 strain RC1 (OLDA) (taken from Ref. 46 and modified^{16,44}).

to two proteins involved in LPS biosynthesis in *P. aeruginosa* IATS serotype O5⁴⁹ and *L. pneumophila*.⁴⁷ The *wbpG* gene of *P. aeruginosa* O5 is thought to encode an aminotransferase responsible for synthesis of the acetimidoyl group at N-3 of a 2,3-diamino-2,3-dideoxy-D-mannuronic acid residue in OPS.⁴⁹ The gene termed ORF 28 in *L. pneumophila* is part of an LPS locus involved in the synthesis of polylegionaminic acid⁴⁷ (see below), whose monomer carries an acetamido group at C-5.³¹ It remains unknown at which step in the biosynthesis of pseudaminic acid derivatives the substitution of the *N*-acetyl group with *N*-acetimidoyl group might occur.

b. Legionaminic Acid.—For studies of biosynthesis of legionaminic acid, wild-type strains of *L. pneumophila* serogroup 1 and isogenic LPS mutants were used,⁴⁷ all containing a homopolymer OPS composed of 5-*N*-acetimidoyl-7-*N*-acetyllegionaminic acid³¹ (structure 17 in Fig. 5).

Complementation of a spontaneous LPS mutant (mutant 137) with a genomic library prepared from *L. pneumophila* serogroup 1 strain 5097 (OLDA) restored the wild-type LPS phenotype. A 32.6 kb DNA fragment that contained 30 ORFs (Fig. 9) was found to be responsible for the complementation. The locus includes ORFs with significant homology to genes encoding enzymes required for the biosynthesis of LPS or polysaccharide capsule of Gram-negative bacteria. The entire locus is present in *L. pneumophila* serogroup 1 strains whereas only its parts are present in strains of other serogroups, which contain as OPS homopolymers of 4-epilegionaminic acid or isomers not yet identified (Section II.2). In addition to genes likely involved in LPS core biosynthesis and LPS assembly, there were genes that encode putative enzymes of legionaminic acid biosynthesis (*mnaA*, *neuB*, and *neuA*).

The amino acid sequence deduced from ORF 23 (*mnaA*) shared homology with bacterial *N*-acetylglucosamine 2-epimerases that convert *N*-acetylglucosamine into *N*-acetylmannosamine, a precursor of sialic acids. ORF 9 and ORF 24 (*neuB*) both produce polypeptides that exhibited 25 and 31%

identity, respectively, to the SiaC protein of *Neisseria meningitidis*, an enzyme that mediates condensation of *N*-acetylmannosamine and enolpyruvate phosphate. The reason for the existence of two genes that encode SiaC homologues is unknown. The predicted polypeptide encoded by ORF 25 (*neuA*) revealed striking homology to other bacterial CMP-Neu5Ac synthases. This class of enzymes catalyzes the synthesis of CMP-*N*-acetylneuraminic acid, which is subsequently polymerized to form polysialic acid.

The *neuA* (ORF 25) and *neuB* (ORF 24) gene products were functionally characterized by complementation of *E. coli* K1 mutants EV5 and EV24 that are defective in K1 polysialic acid capsule biosynthesis. The EV5 mutant was complemented to wild-type capsule production by introduction of *neuA*, and the EV24 mutation complemented by the *neuB* gene.

Based on these findings, it is likely that ORFs 23, 24, and 25 encode enzymes that play a role in biosynthesis and polymerization of legionaminic acid and that the biosynthetic pathway is similar to that of bacterial sialic acid-containing polysaccharides.¹ ORFs that encode putative legionaminic acid transferase or polymerase were not found in the 32.6-kb locus.

The ORF 28 gene product showed similarity to PseA, a putative aminotransferase responsible for the synthesis of the *N*-acetimidoyl group on pseudaminic acid in *C. jejuni* flagellin.¹⁶ ORF 28 might be thus involved in conversion of the 5-*N*-acetyl group on legionaminic acid into the 5-*N*-acetimidoyl group.

ORFs 8–12 comprise an operon that is present only in serogroup 1 strains of *L. pneumophila*.⁴⁷ The deduced amino acid sequence of ORF 8 revealed homology (45–52%) to bacterial methyltransferases. Expression of the ORF 8 gene in LPS mutant 137 restored binding of mAb 2625 (Section II.4), which is specific for *N*-methylated legionaminic acid residues **19** and **20** in long-chain OPS⁴⁴ (Section II.1, Fig. 5). Therefore, it was suggested that the ORF 8 gene encodes methyltransferase that is responsible for *N*-methylation of the acetamidino group at position 5 of legionaminic acid.

Interestingly, the LPS epitope recognized by mAb 2625⁴³ and *N*-methylation of legionaminic acid⁴⁴ is lost upon phase variation in *L. pneumophila* serogroup 1. Phase variation was found to be dependent upon chromosomal excision and replication of a high-copy plasmid.⁵⁰ DNA sequencing of the 30 kb episome did not reveal any genes with homology to LPS or another surface polysaccharide biosynthesis genes. Therefore, phase variation of serogroup 1 LPS must be mediated by an indirect mechanism, possibly by involvement of a regulatory factor whose normal function might be inhibited by a gene product encoded on the episome.

Using Tn5 mutagenesis, complementation analysis, and DNA-sequencing experiments, a gene designated *lag-1* (lipopolysaccharide-associated gene)

that is involved in 8-*O*-acetylation of legionaminic acid was identified in Pontiac-group strains of *L. pneumophila* serogroup 1.^{51,52} *lag-1* mutants, CS332 and TF 3/1 from strains Philadelphia 1⁵¹ and Corby,⁵² respectively, lost the ability to produce 8-*O*-acetylated polylegionaminic acid and to bind mAb 2 and mAb 3/1 (see Section II.4). Complementation of both mutants with a wild-type *lag-1* gene restored 8-*O*-acetylation and mAb binding. Introduction and expression of this gene in the non-Pontiac-group OLDA strain that normally does not carry *lag-1* resulted in production of 8-*O*-acetylated polylegionaminic acid.⁴²

The Philadelphia 1 *lag-1* gene encodes a 357-amino-acid protein that exhibited strong homology (54% identity) with Oac, a membrane-anchored *O*-acetyltransferase from bacteriophage SF6 of *Shigella flexneri*.⁵¹ The *lag-1* locus from strain Corby exhibited 89.6% similarity at the nucleotide sequence level and 91.3% similarity in amino acid sequence to the Philadelphia 1 *lag-1* gene. The mutant *lag-1* gene present in the Corby TF 3/1 LPS mutant contained a single nucleotide change at position 169 that caused an amino acid change from serine to a leucine in a highly conserved motif present in many bacterial *O*-acetyltransferases. This change is apparently responsible for the loss of enzymatic activity of Lag-1 encoded by the mutant gene.⁵²

Upstream and downstream genes adjacent to the Corby *lag-1* gene correspond to ORF 2 and ORF 3 on the 32.6 kb LPS biosynthesis locus described in strain OLDA⁵² (Fig. 9). The *lag-1* gene is found at various chromosomal locations in different Pontiac-group isolates,⁵³ which suggested that *lag-1* may be contained in an unstable genetic element.

Interestingly, in short-chain OPS, the first three legionaminic acid residues located next to the LPS core are 8-*O*-acetylated in all *L. pneumophila* serogroup 1 strains, whether they contain *lag-1* or not.⁴² This suggested that there must be another gene different from *lag-1* that encodes a second *O*-acetyltransferase with specificity for both the position of the legionaminic acid residue and OPS chain length. *lag-1*-Independent *O*-acetylation seems to prevent *N*-methylation of legionaminic acid in short-chain OPS (see above), whereas *lag-1*-dependent *O*-acetylation of long-chain OPS does not interfere with *N*-methylation. This is likely due to the notion that *lag-1*-dependent *O*-acetylation occurs after *N*-methylation. A likely candidate for the second *O*-acetyltransferase-encoding gene is ORF 22 found in the 32.6 kb locus (Fig. 9). A portion of ORF 22 that corresponded to amino acid positions 100–210 of the deduced ORF 22 gene product exhibited homology to cytoplasmic acetyltransferases but no homology to Lag-1.⁴⁷ However, it is not excluded that ORF 22 rather play a role in *O*-acetylation of LPS core monosaccharides.

4. Role in the Immunospecificity of Bacterial Antigens

LPSs carry the major immunogenic determinants on the cell surface of Gram-negative bacteria and, in many instances, serve as the basis for their serological classification. In this section, contribution of LPSs that contain 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acids to the immunospecificity and serological classification of two human pathogens, viz. *L. pneumophila* and *P. aeruginosa*, are reviewed.

a. *Legionella pneumophila*.—Derivatives of 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acid isomers that are present in OPSs of all *L. pneumophila* serogroups,^{11,31,40} constitute multiple antigenic determinants and serve as the basis for serotyping. Strains of *L. pneumophila* are divided into at least 15 serogroups with rabbit polyclonal antisera⁵⁴ and 64 subgroups with mAbs.⁵⁵ Serogroups 1 and 7 exhibited no serological cross-reactivity with serogroup-specific mAbs.⁵⁵ This finding is consistent with the presence of legionaminic acid^{11,31} and an unidentified isomer of legionaminic acid⁴⁰ in OPSs of serogroups 1 and 7, and only in these OPSs, respectively. In contrast, all other serogroups exhibited cross-reactivity with various serogroup-specific mAbs.⁵⁵ This is likely due to the existence of common or cross-reactive epitopes formed by 4-epilegionaminic acid, which is present in OPSs of all serogroups except 1 and 7.⁴⁰ The chemical basis for classification of *L. pneumophila* strains to different cross-reactive (non-1, non-7) serogroups remains unknown.

Clinical isolates of *L. pneumophila* serogroup 1 can be subdivided into 15 mAb subgroups⁵⁵ but the epitope specificity of only a few of these mAbs has been determined. One of them is mAb 3/1 (or mAb 2), which recognizes a major epitope on polylegionaminic acid associated with the 8-*O*-acetyl group.⁵⁶ The reactivity is lost after chemical removal of the *O*-acetyl group⁵⁶ or as a result of a mutation in the *lag-1* gene^{51,52} that makes this mAb a useful tool for differentiation between functional *lag-1*-positive (Pontiac group) and -negative (non-Pontiac group) strains (see also [Section II.3](#)). The loss of the mAb 3/1 epitope in serogroup 1 OPS was accompanied by binding of some other LPS-specific mAbs that were unable to bind to OPS that contained the mAb 3/1 epitope.^{52,56} This suggested that the 8-*O*-acetyl group that binds mAb 3/1 blocks the access to some other mAb epitopes present on polylegionaminic acid.

Binding of mAb 2625 to serogroup 1 isolates was found to correlate with *N*-methylation of the 5-acetimidoylamino group on a single legionaminic acid residue in OPS⁴⁴ (structures **19** and **20** in [Fig. 5](#)). Saturation-transfer-difference NMR spectroscopy showed that the binding of mAb 2625 is mainly mediated via the *N*-methylated 5-acetimidoylamino group in both

19 and **20** and via the closely located 7-acetamido group of the same legionaminic acid residue, thus confirming the *N*-methylated derivatives of legionaminic acid to represent the major epitope of mAb 2625.⁵⁷ In Pontiac group strains, this epitope is masked by the presence of the 8-*O*-acetyl group of legionaminic acid but becomes accessible to the antibody binding after chemical de-*O*-acylation of LPS.⁴⁴ The mAb 2625 epitope is lost upon inactivation of ORF 8 that encodes a putative methyltransferase⁴⁷ (see Section II.3). Binding of mAb 2625 interferes with binding of mAb LPS-1, an antibody that recognizes a highly *O*-acetylated outer-core region of serogroup 1 LPS. This suggested that the mAb 2625 epitope is located close to the core region.⁴⁴

The 8-*O*-acetyl-associated epitope of legionaminic acid was also found in *P. fluorescens* ATCC 49271, which has the same OPS structure **17** as *L. pneumophila* serogroup 1^{32,56} (Fig. 5). This epitope, possibly along with other, yet uncharacterized cross-reactive epitopes, is likely responsible for the serological cross-reactivity exhibited by *P. fluorescens* and distantly related *L. pneumophila*.

b. *Pseudomonas aeruginosa*.—The presence or absence of the *O*-acetyl group at position 4 of pseudaminic acid is responsible for the subdivision of *P. aeruginosa* serogroup O9 into two subgroups, O9a and O9a,9b²² (Section II.2, Fig. 2). Epitope O9b in the latter is evidently associated with the 4-*O*-acetyl group.

A role of the 5-*N*-acyl group of pseudaminic acid in serospecificity was demonstrated in studies of *P. aeruginosa* serogroup O7 strains, which could be divided into three subgroups: O7a,7b,7c, O7a,7b,7d, and O7a,7d (Section II.2, Fig. 3). It was concluded that epitopes O7c and O7d are linked to the 5-*N*-[(*R*)-3-hydroxybutanoyl] and 5-*N*-acetyl group, respectively.²³

A remarkable antigenic similarity between LPS and pilin of *P. aeruginosa* 1244 was recognized using a polyclonal typing serum to LPS of *P. aeruginosa* O7 and mAb 11.14.¹⁶ This was substantiated by modification of pilin with an O-linked pseudaminic acid-containing trisaccharide (**11**), which is identical or closely related to the OPS repeating unit (Section II.2, Fig. 3). It was demonstrated that the mAb 11.14-reactive epitope is present on the pilus surface under physiological conditions,¹⁶ and, therefore, like the O-chain polysaccharide of LPS, the oligosaccharide chain of pilin may contribute to the O7 immunospecificity. It is likely that both antigens have a common biosynthetic origin, and thus the pseudaminic acid derivative in OPS of *P. aeruginosa* O7 occupies the terminal nonreducing position most accessible to specific antibodies.

A cross-reactivity was reported between *P. aeruginosa* serogroups having LPSs that contain 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulonic acids and some enterobacteria.^{58,59} A close structural similarity of OPSs of *P. aeruginosa* O12 and *Salmonella arizonae* O61,⁵⁸ which both contain 8-epilegionaminic acid (**24** and **26**), is evidently responsible for the serological relatedness of these bacteria.³⁷ In contrast, OPSs of serologically related⁵⁹ bacteria *P. aeruginosa* O9a and *Shigella boydii* type 7 are different (compare structures **6**²² and **12**,²⁴ Section II.2) and have a β -linked pseudaminic acid derivative as the only monosaccharide in common. Most likely, in this case the cross-reactivity is due to the presence of the common sugar at the terminal nonreducing end of the OPS chain in both bacteria.

5. Possible Biological Significance

a. Polylegionaminic Acid.—*Legionella pneumophila* is an intracellular pathogen that invades and multiplies in mononuclear phagocytes of mammalian hosts. Legionaminic acid in OPS of *L. pneumophila* serogroup 1 has the same configuration and the same ²C₅ ring conformation as neuraminic acid, a common constituent of mammalian host-cell-surface glycoconjugates. Therefore, it is possible that the structural similarities between polylegionaminic acid present on the *L. pneumophila* cell surface and sialic acid-containing glycoconjugates on host cells enable legionellae to escape the immune response of an infected host. On the other hand, the similarity between legionaminic and neuraminic acids might make *L. pneumophila* the target of eukaryotic sialidases. It is possible that the *N*-acetyl, *N*-acetimidoyl, and *O*-acetyl groups enhance the resistance of polylegionaminic acid to eukaryotic sialidases and aid the intracellular persistence of the microorganism in infected host cells.⁶⁰

Due to the negative charge of the carboxyl groups and positive charge of the *N*-acetimidoyl groups, polylegionaminic acid may be involved in binding of ions and regulation of the outer-membrane permeability. Attraction and repulsion between polylegionaminic acid and other cell-surface components may stabilize the conformation of the macromolecules and the outer membrane as a whole. On the other hand, the presence of the deoxy groups and *N*- and *O*-acyl substituents in polylegionaminic acid makes LPS of *L. pneumophila* highly hydrophobic.⁶⁰ The hydrophobicity of the bacterial surface may promote the adherence to alveolar macrophages, an early step of pulmonary infection by the bacterium.

The majority of clinical isolates, in particular strains associated with *L. pneumophila* outbreaks, were found to bind mAb 2 and mAb 3/1. This has led to the notion that the 8-*O*-acetyl-associated epitope of legionaminic

acid is associated with virulence.⁵⁶ However, infection experiments showed no discernible difference in uptake or intracellular multiplication of *lag-1*-positive strains and the corresponding isogenic *lag-1* mutants in monocyte-like U937 cells, guinea pigs alveolar macrophages, and free-living amoebae.^{52,61} Nevertheless, 8-*O*-acetylation of polylegionaminic acid may contribute to virulence by promotion of the spread of the bacterium during *L. pneumophila* outbreaks. Aerosolization of contaminated water, mainly the condensing water of cooling towers, has been shown to be the major source of transmission during outbreaks of community-acquired Legionnaires' disease. 8-*O*-Acetylation increases the hydrophobicity of LPS and thus enhances the ability of the microorganism to form stable aerosols. In support of this idea, it was found that mAb 3/1 bound to 26 of 30 clinical isolates from community-acquired cases but only to 10 of 23 nosocomial isolates.⁵²

b. Glycoproteins.—Pilin of *P. aeruginosa*¹⁵ and *Campylobacter* flagellins¹⁶ are involved in carrying out motility and other surface protein-dependent functions of bacteria involved in pathogenesis. Mutations of *neuB3*, a putative gene involved in biosynthesis of pseudaminic acid in *C. jejuni* flagellin, resulted in loss of motility.⁶²

Glycosylation of the proteins has the potential to influence the interaction of the cell with its environment. The presence of negatively charged pseudaminic acid derivatives on the surface would lower the isoelectric point, influence solubility, and likely increase ionic interactions.¹⁵ In *C. jejuni* flagellin, these may be further controlled by introduction of a basic acetamidino group to the sugar.¹⁶

Pseudaminic acid derivatives may function as a biological mask protecting sensitive protein structures from proteolytic cleavage. A structural similarity between pseudaminic and sialic acids may play a role in immune avoidance by protecting the proteins from complement binding and phagocytosis, or from the host B-cell response. This may also account for binding of a sialic acid-specific lectin to *Campylobacter* flagellins.¹⁶

III. CHEMICAL SYNTHESIS AND STRUCTURE DETERMINATION

The main approaches used for identification of natural isomers of 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acids and determination of structures of bacterial poly- and oligosaccharides-containing derivatives of these sugars were ¹H and ¹³C NMR spectroscopy. This could be applied to both intact natural glycopolymers and carbohydrate portions obtained after delipidation of LPS as well as to oligosaccharide fragments and

monosaccharides prepared by chemical degradations. Complementary and sometimes essential information could be obtained using mass spectrometry of oligosaccharides and open-chain derivatives of monosaccharides. The most complex problem was the full configuration assignment. Whereas the relative configuration of the chiral centers within the pyranose ring (C-4–C-6) could be easily established using ^1H NMR spectroscopy (see later), determination of the configuration in the side chain (C-7–C-8) was accomplished after chemical synthesis of various stereoisomers with fully defined configurations.

1. Chemical Synthesis

By analogy with the synthesis of *N*-acetylneuraminic acid,⁶³ di-*N*-acetyl derivatives of 5,7-diamino-3,5,7,9-tetradeoxynon-2-ulosonic acids could be obtained by condensation of 2,4-diacetamido-2,4,6-trideoxyhexoses with oxaloacetic acid under basic conditions. Four chiral centers in the C₆ precursors, C-2–C-5, correspond to the centers C-5–C-8 in the target C₉ products, and the fifth asymmetric center, C-4, is formed upon condensation. At present, derivatives of twelve 2,4-diamino-2,4,6-trideoxyhexoses with the *D*-*gluco*, *D*-*manno*, *L*-*allo*, *D*-*galacto*, *D*- and *L*-*altro*, *D*- and *L*-*talo*, *D*- and *L*-*gulo*, *D*- and *L*-*ido* configurations have been prepared by multistep chemical syntheses.^{11,17,18,64,65}

2,4-Diacetamido-2,4,6-trideoxy-*D*-mannose (**30**), -*L*-gulose (**31**), -*D*-talose (**32**), and -*L*-allose (**33**) were used in the synthesis of 5,7-diacetamido-3,5,7,9-tetradeoxynon-2-ulosonic acids.^{11,17,18} The initial C₆ compounds possess the same *L,L* configuration at C-2 and C-3 (corresponding to C-5 and C-6 in the C₉ products), whereas the configurations at C-4 and C-5 vary, thus adopting all possible stereochemical combinations at C-7 and C-8 of the nonulosonic acids (*D,D*; *D,L*; *L,D*; and *L,L*; respectively). The reaction products were isolated by anion-exchange chromatography and isomers separated by reversed-phase HPLC. The results of condensation of **30–33** with oxaloacetic acid are summarized in Fig. 10.

Compounds **30** and **31** having the *threo* configuration of the C-3–C-4 fragment afforded pairs of the C-4 epimers in nearly equal amounts (**34–37**). The products from **30** are derivatives of legionaminic acid (**34**) and 4-epilegionaminic acid (**35**), and one of the products from **31** is a derivative of 8-epilegionaminic acid (**36**). Compounds **32** and **33** having the *erythro* configuration of the C-3–C-4 fragment yielded the expected sugars with an equatorial HO-4 as the major products (**38** and **40**) but no corresponding compounds with an axial HO-4. Instead, the isomers **39**, **41**, and **42** with an axial AcNH-5 were isolated as minor products, which obviously resulted from a base-induced epimerization at C-2 in the starting monosaccharides

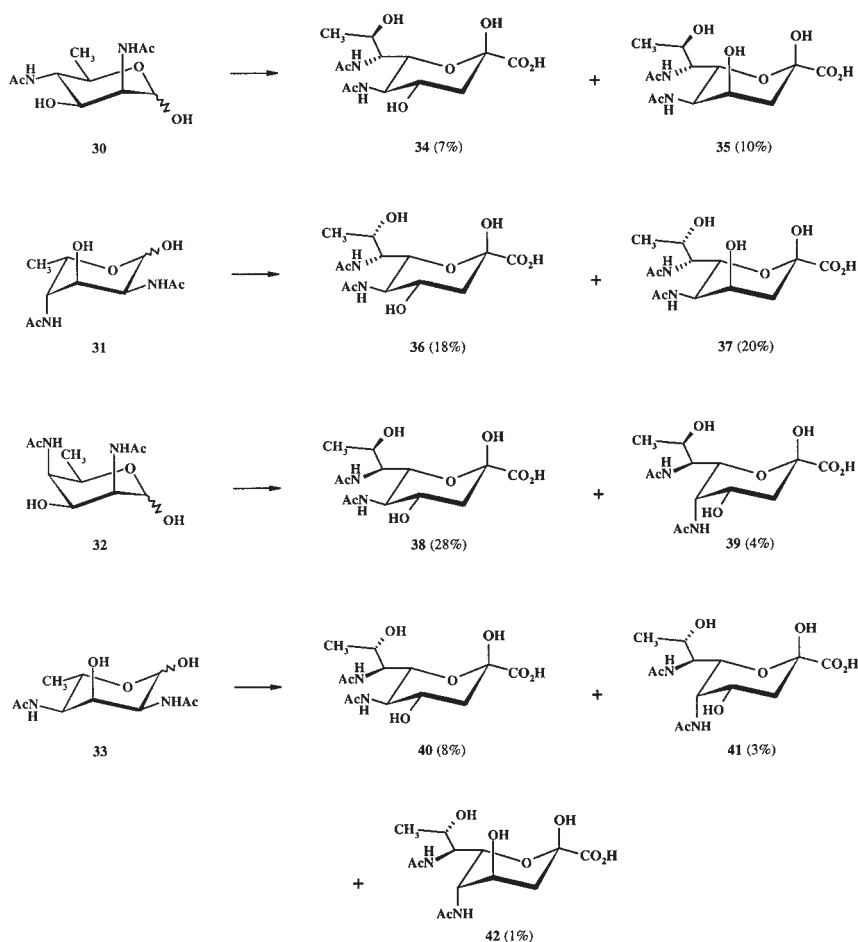


FIG. 10. Chemical syntheses of 5,7-diacetamido-3,5,7,9-tetradexoxynon-2-ulosonic acids (**34–42**) from 2,4-diacetamido-2,4,6-trideoxyhexoses (**30–33**).^{11,17,18} (The reaction conditions: 1.75 mol oxaloacetic acid, 0.4 mol Na₂B₄O₇, pH 10.5, room temperature. The yields of the products are given in parentheses.)

before condensation. A minor product **41** is a derivative of pseudaminic acid. The nonulosonic acids were not obtained in crystalline form and were characterized by optical rotation (Table II) and NMR spectroscopy (Section III.4, Tables III and IV).

To sum up, derivatives of nine isomers of 5,7-diamino-3,5,7,9-tetradexoxynon-2-ulosonic acids having the *D*-glycero-*D*-galacto (**34**),

TABLE II
Ratio of α and β Anomers and Specific Optical Rotation of Synthetic
5,7-Diacetamido-3,5,7,9-tetra-deoxy-non-2-ulosonic Acids

Compound	Configuration	α/β Ratio ^a	$[\alpha]_D$ (°, Water)	References
34	D-glycero-D-galacto	1:18	+27.2	11,18
35	D-glycero-D-talo	1:5.4	-12.5	11,18
36	L-glycero-D-galacto	1:19	+15.4	17,18
37	L-glycero-D-talo	1:8	-19.2	17,18
38	D-glycero-L-altro	13.3:1	-14.3	18
40	L-glycero-L-altro	8.3:1	-48.2	18
39	D-glycero-L-manno	12.5:1	-39.0	18
41	L-glycero-L-manno	7.5:1	-56.9	18
42	L-glycero-L-gluco	4.0:1	-76.0	18

^aThe ratios of α and β anomers are given for solutions in D₂O at 30 °C.

D-glycero-D-talo (35), L-glycero-D-galacto (36), L-glycero-D-talo (37), D-glycero-L-altro (38), D-glycero-L-manno (39), L-glycero-L-altro (40), L-glycero-L-manno (41), and L-glycero-L-gluco (42) configuration have been synthesized, including all four isomers that have been identified as natural compounds. Comparison of the data of the synthetic and natural sugars enabled confirmation of the identity of pseudaminic acid, whereas the configurations of the other isomers were confirmed in some polysaccharides and revised in others.^{11,18}

2. Preparation of Monosaccharides and Oligosaccharides from Bacterial Polysaccharides

In most structural studies of the polysaccharides, oligosaccharides containing the nonulosonic acids were prepared in order to have better-resolved NMR spectra and for investigation by MS. In some examples, a monosaccharide or a monosaccharide glycoside were also prepared by chemical degradations.

a. Solvolysis.—Independent of the anomeric configuration, the glycosidic linkage of the nonulosonic acids was found to be completely stable toward solvolysis, which makes this method most useful for preparation of oligosaccharides with linked residues of the nonulosonic acids.^{22-24,30,36,37,39} Thus, a disaccharide with pseudaminic acid at the nonreducing end (43) was obtained by solvolysis with anhydrous hydrogen fluoride of OPS of *P. aeruginosa* O9a²² (6) (Fig. 11). When solvolysis was performed in the presence of methanol, the products were methyl glycosides of the same disaccharide²² (44). These and other methyl glycosides were found to be

more convenient for isolation by reversed-phase HPLC and subsequent NMR spectroscopic studies compared to free oligosaccharides.^{22,23,30,37} Various oligosaccharides, from di- to tetra-saccharide, or oligosaccharide methyl glycosides were prepared by solvolytic cleavage of some other heteropolysaccharides containing pseudaminic acid [*P. aeruginosa* O7a,7d²³ (10) and *S. boydii* type 7²⁴ (12)] or 8-epilegionaminic acid [*P. aeruginosa* O12³⁰ (24), *Y. ruckerii* O1³⁶ (25), *S. arizonae* O61³⁷ (26), and *S. putrefaciens* A6³⁹ (27)].

Varying the reaction conditions gave rise to larger or smaller oligosaccharides. For instance, the α -D-QuipNAc-(1 \rightarrow 8)- α -8eLegp5Ac7Ac-(2 \rightarrow 3)- α -L-FucpNAc-(1 \rightarrow OMe) trisaccharide or the α -8eLegp5Ac7Ac-(2 \rightarrow 3)- α -L-FucpNAc-(1 \rightarrow OMe) disaccharide were obtained as the predominant products from OPS of *P. aeruginosa* O12 (24) by solvolysis with anhydrous hydrogen fluoride in methanol at 20 and 40 °C, respectively.³⁰

In a recent study of the pseudaminic acid-containing OPS of *P. vulgaris* O39 (15), hydrogen fluoride was successfully replaced with trifluoromethanesulfonic (triflic) acid.²⁸ Again, solvolysis with triflic acid could be performed to give the α -D-GlcpNAc-(1 \rightarrow 8)- β -Psep5Ac7Ac-(2 \rightarrow 3)-L-FucNAc trisaccharide under mild conditions (−4 °C for 2 h) or the β -Psep5Ac7Ac-(2 \rightarrow 3)-L-FucNAc disaccharide under more drastic conditions (20 °C for 16 h).

b. Acid Hydrolysis.—Compared to solvolysis, acid hydrolysis of the polysaccharides proceeded differently and enabled preparation of oligosaccharides with the nonulosonic acids at the reducing end. The rate of hydrolysis of the ketosidic linkage was found to depend significantly on the anomeric configuration. When the carboxyl group is equatorial, as in α -pseudaminic acid^{23,27} or β -legionaminic acid,³⁵ hydrolysis proceeded so easily that the polysaccharide chain depolymerized during delipidation of LPS with dilute aqueous acetic acid^{23,27,35} or sodium acetate buffer at pH 4.2.²¹ Thus, no OPS could be isolated from the α -pseudaminic acid-containing LPS of *P. aeruginosa* O7a,7d (immunotype 6) (10) since aqueous 1% acetic acid at 100 °C cleaved the polysaccharide to the repeating unit trisaccharide²³ (46) (Fig. 12). The CPS from *S. fredii* HH103 (5) was also cleaved under mild acidic conditions, and the resulting mixture of 5-*N*-acetyl-7-*N*-(3-hydroxybutanoyl)pseudaminic acid and its oligomers was fractionated by gel-permeation chromatography on Sephadex G-50 and Sephadex G-15.¹⁴

The hydrolytic cleavage of the glycosidic linkage of the sugars with an axial carboxyl group required more drastic conditions, but even these allowed selective degradation. For instance, selective cleavage of the

TABLE III
¹H NMR Data of Synthetic 5,7-Diacetamido-3,5,7,9-tetradexon-2-ulosonic Acids^a

Configuration (Compound)		H-3eq (<i>J</i> _{3eq,3ax})	H-3ax (<i>J</i> _{3ax,4})	H-4 (<i>J</i> _{3eq,4})	H-5 (<i>J</i> _{4,5})	H-6 (<i>J</i> _{5,6})	H-7 (<i>J</i> _{6,7})	H-8 (<i>J</i> _{7,8})	H-9 (<i>J</i> _{8,9})
D-glycero-D-galacto (34)	α	2.73 (12.9)	1.71 (11.9)	3.82 (4.7)	3.68	3.93 (10.3)		3.94	1.16
	β	2.31 (13.1)	1.87 (11.7)	3.98 (4.8)	3.72 (10.3)	4.31 (10.5)	3.91 (1.9)	3.85 (8.9)	1.16 (6.2)
D-glycero-D-talo (35)	α	2.69 (14.4)	1.94 (3.5)	4.10 (3.0)	3.86 (2.9)	4.55 (10.8)	3.88 (2.3)	4.00 (8.6)	1.20 (6.4)
	β	2.19 (14.9)	2.14 (3.4)	4.13 (3.0)	3.90 (2.9)	4.63 (10.8)	3.92 (<2) ^b	3.92 (8.7) ^b	1.18 (5.5)
L-glycero-D-galacto (36)	α	2.69 (13.0)	1.71 (12.0)	3.82 (4.9)	3.67 (10.4)	3.85 (10.4)	3.93 (1.7) ^b	4.00 (6.4)	1.20 (6.5) ^b
	β	2.32 (13.1)	1.86 (11.5)	3.95 (4.8)	3.73 (10.2)	4.16 (10.3)	3.95 (2.0)	3.91 (6.4)	1.18 (6.2)
L-glycero-D-talo (37)	α	2.65 (14.4)	1.94 (2.7)	4.08 (3.6)	3.84 (2.7)	4.47 (10.5)	3.89 (2.0) ^b	4.08	1.28 (6.3)
	β	2.18 ^c (14.9)	2.13 ^c (3.3)	4.11 (2.9)	3.89 (2.8)	4.48 (10.6)	3.95 (1.3)	3.96 (6.5) ^b	1.21 (5.7)
D-glycero-L-altro (38)	α	2.34 (13.2)	1.93 (11.6)	3.99 (4.8)	3.86 (9.4)	3.90 (10.1)	3.92 (2.8)	4.42 (<1)	1.08 (6.4)
	β	2.71 (12.5) ^b	1.75 (11.1) ^b	3.82 (4.5) ^b	3.81 (9.8) ^b	3.56 (9.8) ^b	3.91 (5.1) ^b	4.40 (1.8) ^b	1.08 (6.3) ^b

L-glycero-L-altro (40)	α	2.32 (13.3)	1.93 (12.5)	3.94 (4.4)	3.91 (10.2)	3.94 (10.2)	4.16 (2.8)	4.06 (5.8)	1.18 (6.4)
	β	2.70 (12.8)	1.72 (12.2)	3.79 (4.5)	3.85 (10.7)	3.57 (10.7)	4.13 (3.3)	4.07 (6.0)	1.21 (6.3)
D-glycero-L-manno (39)	α	2.03 (13.4)	1.82 (12.3)	4.25 (5.0)	4.29 (4.3)	4.27 (1.8)	3.82 (10.1)	4.12 (1.2)	1.09 (6.6)
	β	2.50 (13.2)	1.64 (12.8)	4.10 (4.9)	4.22 (4.5)	4.14 (2.1)	3.86 (10.4)	4.25 (1.6)	1.10 (6.4)
L-glycero-L-manno (41)	α	2.01 (12.8)	1.80 (12.0)	4.20 (4.6)	4.27 (3.7)	4.08 (1.0) ^b	4.17 (10.7)	4.10 (3.3)	1.10 (6.5)
	β	2.48 (13.0)	1.62 (12.9)	4.08 (4.7)	4.29 (3.6)	3.96 (2.4)	4.15 (10.5)	4.18 (3.4)	1.12 (3.4)
L-glycero-L-gluco (42)	α	1.95 (15.2)	2.13 (3.6) ^b	4.00 (3.7)	3.91 (3.3)	4.42 (2.1)	4.22 (10.5)	4.16 (3.5)	1.15 (6.6)
	β	2.48 (14.8)	1.92 (2.9)	4.00 (3.1)	3.85 (2.6)	4.36 (2.2)	4.15 (10.3)	4.24 (4.0)	1.21 (6.5)

^aChemical shifts in ppm at 500 MHz, coupling constants in Hz for solutions in D₂O at 30 °C. Signals for the *N*-acetyl groups are at δ 1.95–2.08. Refs. 11, 17, 18.

^bData of sodium salt.

^cAssignment could be interchanged.

TABLE IV
¹³C NMR Data of Synthetic 5,7-Diacetamido-3,5,7,9-tetradexonon-2-ulosonic Acids^a

Configuration (Compound)		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
D-glycero-D-galacto (34)	α		97.2	41.4	69.2	53.4	73.2	54.4	68.0	20.4
	β	174.4 ^b	96.6	40.3	68.4	53.9	70.9	54.4	67.5	20.4
D-glycero-D-talo (35)	α			40.2	66.9	49.7	70.3	55.0	68.2	19.8
	β	174.7 ^b	96.3	37.6	67.1	49.7	66.5	54.7	67.2	20.4
L-glycero-D-galacto (36)	α	173.1	97.3	41.2	68.9	53.7	75.2	54.4	69.4	19.8
	β	174.3	96.5	40.4	68.3	54.1	72.9	54.4	69.3	19.8
L-glycero-D-talo (37)	α			40.0	66.6	50.1	72.6	54.9	69.7	19.9
	β	174.5 ^b	96.1	37.7	66.9	50.0	68.5	54.9	69.2	19.9
D-glycero-L-altro (38)	α	173.7	96.1	39.9	67.6	54.7	75.7	53.9	66.6	20.2
	β	172.9	97.2	41.1	68.7	54.7	77.3	54.3	66.5	20.0
L-glycero-L-altro (40)	α	173.7	96.1	39.9	68.2	55.3	73.7	55.5	67.6	19.7
	β	173.0	97.0	41.2	69.1	54.9	76.0	55.8	67.8	19.7
D-glycero-L-manno (39)	α	174.7	96.8	35.5	66.1	49.9	70.3	54.4	66.0	20.0
	β			36.8	68.0	49.1	73.0	54.4	67.4	20.0
L-glycero-L-manno (41)	α	174.9	97.0	35.6	66.1	49.9	71.4	54.0	68.1	16.7
	β			36.7	67.3	49.9	74.3	53.8	68.2	16.7
L-glycero-L-gluco (42)	α	174.6	96.4	33.3	67.1	48.9	67.1	53.8	67.9	16.6
	β			35.7	67.4	48.5	71.8	54.4	68.6	17.0

^aChemical shifts in ppm at 125 MHz for solutions in D₂O at 30 °C. Signals for the *N*-acetyl groups are at δ 22.9–23.5 (CH₃) and 174.2–175.9 (CO). Refs. 11, 17, 18.

^bAssignment of the signals for CO₂H of the sugar and CO of the *N*-acetyl groups could be interchanged.

glycosidic linkage of α -8-epilegionaminic acid in OPSs of *Y. ruckeri* O1³⁶ (25) and *S. arizonae* O61³⁷ (26) was performed with 0.1 *M* HCl at 95 or 100 °C for 5 h and resulted in tri- and tetrasaccharides. Similar hydrolysis of the α -D-GlcpNAc-(1 \rightarrow 8)- α -8eLegp5(R3Hb)7Ac-(2 \rightarrow 3)- α -L-FucpNAc-(1 \rightarrow OMe) trisaccharide obtained by solvolysis of the polysaccharide 26 afforded the α -D-GlcpNAc-(1 \rightarrow 8)-8eLegp5(R3Hb)7Ac disaccharide and α -L-FucpNAc-(1 \rightarrow OMe) glycoside.³⁷

In contrast, the homopolymers of 5-*N*-acetimidoyl-7-*N*-acetyl- α -legionaminic (17) and -4-epilegionaminic (18) acids present in LPS of *L. pneumophila* were found to be stable toward acid hydrolysis.^{31,40} Attempts to isolate monomers by methanolysis or solvolysis with hydrogen fluoride also failed, and only minor amounts of chiral alcohol derivatives for determination of the absolute configurations by GLC–MS could be prepared by acid alcoholysis with (*S*)-2-butanol.^{11,40} Conversion of the *N*-acetimidoyl group to the *N*-acetyl group was necessary for the cleavage of polylegionaminic acid 17 but not poly(4-epilegionaminic) acid 18. The conversion in the polymer 17 required rather drastic alkaline conditions (0.1 *M* NaOH, 100 °C, 5 h).³¹ Other oligo- and polysaccharides containing

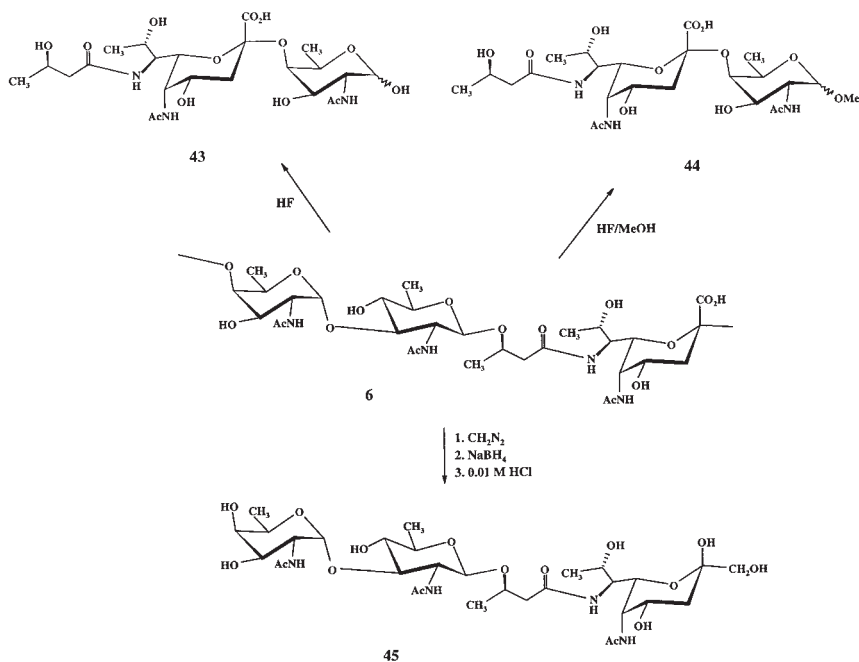


FIG. 11. Selective cleavages of OPS of *Pseudomonas aeruginosa* O9a (6).²²

N-acetimidoyl derivatives of the nonulosonic acids, including the polymer **18**, could be hydrolyzed to the corresponding *N*-acetyl derivatives by treatment with a weak aqueous base, e.g., 12% ammonia (80 °C, 16 h or 45 °C, 4 h),^{32,40} 5% triethylamine (60 °C, 16 h),²⁵ or Na_2CO_3 at pH 12 (20 °C, 14 days).³⁹

Carboxyl reduction of a nonulosonic acid with an axial carboxy group facilitated the cleavage of the glycosidic linkage. While the β -pseudaminic acid-containing OPS of *P. aeruginosa* O9a (**6**) was stable toward hydrolysis with 0.01 *M* hydrochloric acid (100 °C, 2 h), the carboxyl-reduced polysaccharide smoothly afforded under these conditions a trisaccharide with the carboxyl-reduced sugar at the reducing end²² (**45**) (Fig. 11). The preferred carboxyl-reduction procedure was found to be borohydride reduction of a methyl ester of the nonulosonic acid, whereas the use of the carbodiimide method resulted in a complex mixture of products.²²

In most cases, the nonulosonic acids present in heteropolysaccharides could not be released as monosaccharides by direct acid hydrolysis because of their instability under the drastic conditions that were necessary to cleave the aldosidic linkage of the neighboring sugar residue. A combination of solvolysis with hydrogen fluoride and acid hydrolysis of the resulting

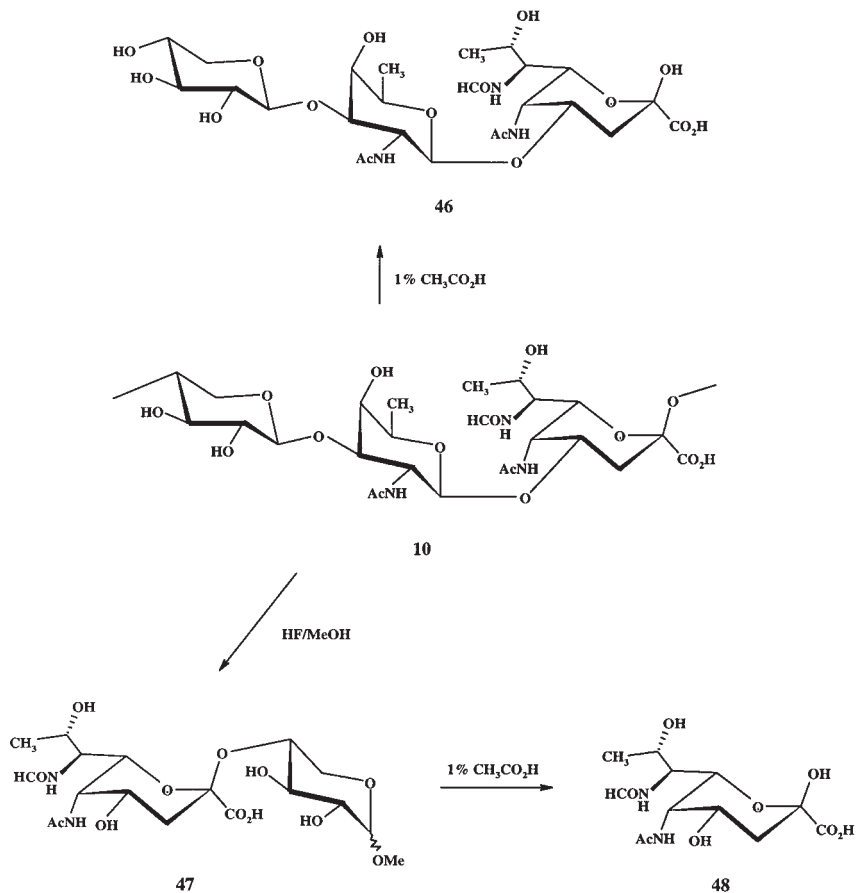


FIG. 12. Selective cleavages of OPS of *Pseudomonas aeruginosa* O7a,7d (10) and preparation of 5-N-acetyl-7-N-formylpseudaminic acid (48).²³

oligosaccharide(s) containing the nonulosonic acid at the nonreducing end provided a way to overcome this difficulty. Thus, 5-N-acetyl-7-N-formylpseudaminic acid (48) was obtained as monosaccharide by hydrolysis with 1% acetic acid (100 °C, 1 h) of disaccharide glycosides (47) prepared by solvolysis of LPS of *P. aeruginosa* O7a,7d (10) with hydrogen fluoride in methanol²³ (Fig. 12).

Solvolysis with the same mixture of OPS of *S. putrefaciens* A6 (29) followed by mild alkaline treatment of the product (49) and hydrolysis of the resultant disaccharide glycoside (50) with 0.5 M $\text{CD}_3\text{CO}_2\text{D}$ in D_2O (100 °C, 6.5 h, with NMR control) released a 2,8-anhydro derivative of 8-epilegionaminic acid with a deuterated methylene group (51), together

with a methyl furanoside of shewanellose (**52**)³⁹ (Fig. 13). The same derivative was obtained from synthetic 8-epilegionaminic acid by hydrolysis under similar conditions.³⁹

c. Smith Degradation.—Three repeated Smith degradations of OPS of *S. boydii* type 7 (**12**) gave, via two oligosaccharides, an ethylene glycol glycoside of β -pseudaminic acid.²⁴ Following conversion of the 5-*N*-acetimidoyl group into the 5-*N*-acetyl group, Smith degradation of OPS of *V. cholerae* O2 (**13**) gave β -D-QuipNAc-(1 \rightarrow 4)- β -Psep5Ac7Ac-(2 \rightarrow 2)-threitol.²⁵ Methanolysis of the same modified polysaccharide gave a β -Psep5Ac7Ac-(2 \rightarrow 4)-D-Gal disaccharide derivative, which upon saponification and Smith degradation yielded a tetritol glycoside of β -pseudaminic acid.²⁵

d. Cyclization in Oligosaccharides.—Under certain conditions, the nonulosonic acids can form interresidue spiro-lactones or-lactams. Thus, lactonization between the residues of di-*N*-acetyllegionaminic acid and *N*-acetylglucosamine to a 1,4-dioxane structure (**53**) was observed on dephosphorylation of the oligosaccharide **21** from *P. fluorescens* ATCC 49271 with aqueous 48% hydrofluoric acid (30 °C, 4 h) following treatment with aqueous ammonia³² (Fig. 14).

Acetylation of a disaccharide glycoside (**54**), prepared by solvolysis of OPS of *P. aeruginosa* O12 (**24**) with hydrogen fluoride in methanol (see above), was accompanied by lactam formation between residues of di-*N*-acetyl-8-epilegionaminic acid and *N*-acetimidoylglucosamine.³⁰ Upon de-*O*-acetylation of the resulting tricyclic disaccharide **55** with 1 *M* NaOMe in methanol (20 °C, 48 h), the *N*-acetimidoyl group was cleaved with no effect on the six-membered lactam ring to yield disaccharide **56** (Fig. 15).

3. Mass Spectrometry

a. Soft Ionization MS.—Soft ionization FAB, ESI, or MALDI mass spectra were obtained for a number of the nonulosonic acid-containing oligosaccharides derived from the glycopolymers (Section III.2). Thus, the FAB mass spectrum of the disaccharide **49** from OPS of *S. putrefaciens* strain A6 (Fig. 13) demonstrated not only the nature of the higher sugars but also that the 8-epilegionaminic acid residue had one *N*-acetyl and one *N*-acetimidoyl group.³⁹ The negative-mode ESI mass spectrum of the oligosaccharide fraction obtained on acid treatment of OPS of *Pseudoalteromonas distincta* KMM 638 showed the presence of a pentasaccharide containing all components of the OPS repeating unit and confirmed the presence of one *N*-acetyl and one *N*-formyl group on the

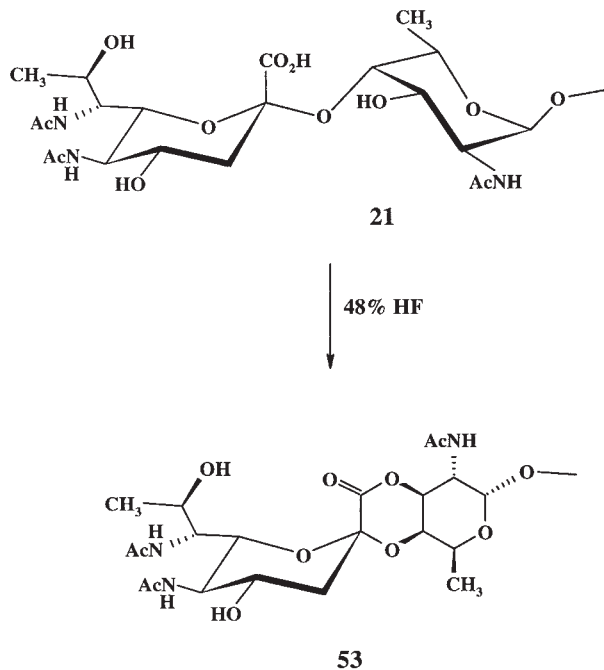


FIG. 14. Lactonization in the oligosaccharide from LPS of *Pseudomonas fluorescens* ATCC 49271 (**21**) upon treatment with aqueous 48% hydrofluoric acid.³² (For the full structure of the oligosaccharide **21**, see Fig. 6.)

pseudaminic acid residue.²⁷ MALDI-TOF MS on an oligomeric fraction derived from the homopolysaccharide **5** of *S. fredii* HH103 (Fig. 2) gave the molecular mass of the repeating unit established as the average difference between clusters formed from several sodium adduct ions.¹⁴

Positive-mode ESI MS-MS analysis was applied to tryptic glycopeptides from *C. jejuni* flagellin for identification of the glycosyl groups.¹⁶ Second-generation fragment ions with m/z 317, 316, and 409 formed by collision-induced dissociation (CID) were consistent with di-*N*-acetyl, *N*-acetimidoyl-*N*-acetyl, and di-*N*-glyceroyl derivatives of pseudaminic acid. The product ion with m/z 316 showed prominent losses of NH_3 and $\text{C}_2\text{N}_2\text{H}_6$ confirming the presence of an acetamido group, and the occurrence of side-chain fragment ions common to both Pse5Ac7Ac and Pse5Am7Ac suggested that the acetamido group was located at position 5 rather than 7.

FAB with CID was applied for sequence determination of the oligosaccharide **22** derived from LPS of *V. salmonicida*³⁴ (Fig. 6). Using the pseudomolecular ion, $[\text{M} + \text{H}]^+$, as precursor ion, several fragments due to cleavage of the glycosidic linkages, including the ketosidic linkage of

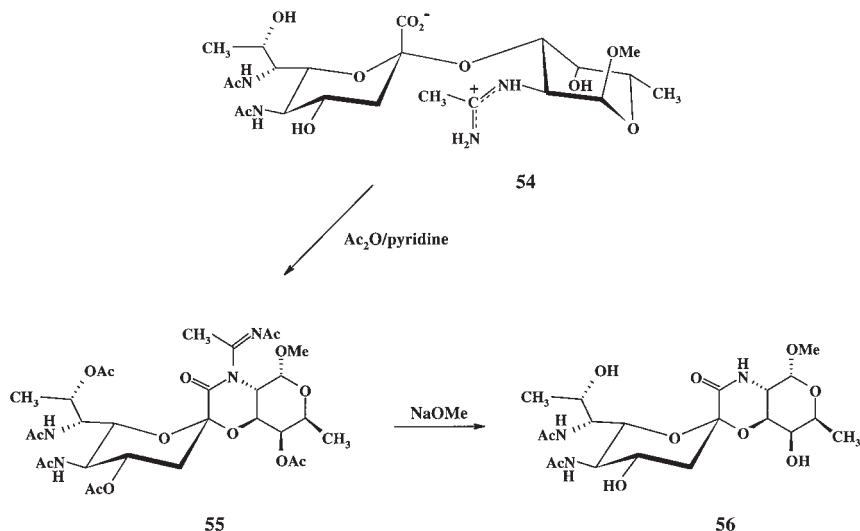


FIG. 15. Formation of lactam upon acetylation of the disaccharide (**54**) from OPS of *Pseudomonas aeruginosa* O12 (structure **24**, Fig. 7) and cleavage of the *N*-acetylacetimidoyl group upon de-*O*-acetylation of the resultant disaccharide (**55**).³⁰

legionaminic acid, (B- and Y-type fragments) were observed in the B/E-linked scan FAB mass spectrum (Fig. 16). Positive-mode FAB MS of a tetrasaccharide with 8-epilegionaminic acid at the reducing end (**57**) from OPS of *Y. ruckerii* O1 (Fig. 7, structure **24**) showed, in addition to $[M + H]^+$, B- and Y-type fragment ions (Fig. 16), and thus in this case no CID was necessary.³⁶ The monosaccharide sequence in the O-linked trisaccharide chain of *P. aeruginosa* pilin with pseudaminic acid at the nonreducing end was confirmed by positive-mode ESI MS–MS of the oligosaccharide–serine **11** isolated from proteolytically digested pure pili.¹⁵ Upon CID, the pseudomolecular ion $[M + H]^+$ afforded B-type fragment ions due to the successive losses of Ser, FucNAc–Ser, and Xyl–FucNAc–Ser (Fig. 16).

b. Electron Impact MS.—In early studies, molecular masses of oligosaccharides were determined by electron impact MS of the acetylated derivatives. For instance, the chemical modification of the disaccharide **54** from OPS of *P. aeruginosa* O12, namely the formation of the spiro-lactam **55** and cleavage of the *N*-acetimidoyl group on alkaline treatment (Fig. 15), were monitored in this way.³⁰ Fragmentation was observed due to losses of the C-8–C-9 fragment, of the methoxycarbonyl group of 8-epilegionaminic acid, and cleavage of the ketosidic linkage.

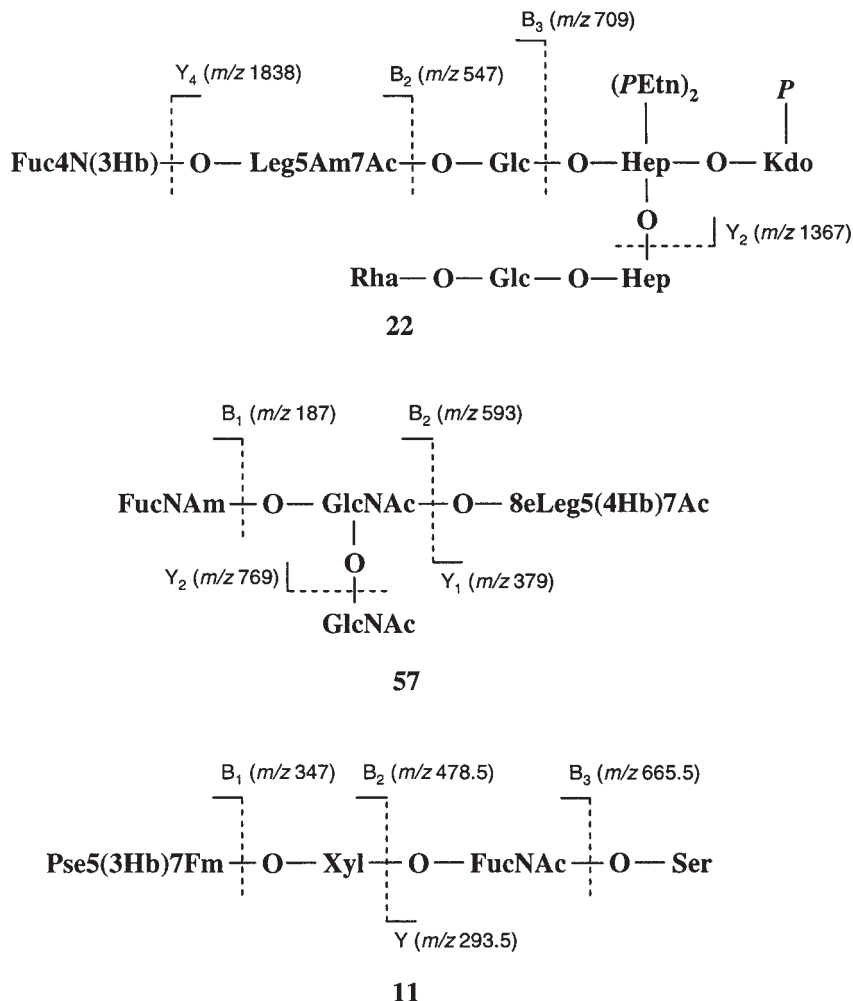


FIG. 16. Fragmentation in FAB MS–MS of the oligosaccharide (**22**) from LPS of *Vibrio salmonicida*,³⁴ FAB MS of the oligosaccharide (**57**) from OPS of *Yersinia ruckerii* O1,³⁶ and ESI MS–MS of the trisaccharide-serine (**11**) from pilin of *Pseudomonas aeruginosa* 1244.¹⁵ (For abbreviations, see Figs. 3, 5, and 7. Pseudomolecular ions $[M+H]^+$ at m/z 1867.6 and 771.5 were used as precursor ions in analysis of **22** and **11**, respectively.)

Electron impact MS of open-chain monomeric derivatives was useful for both determination of the position of acylamino groups and linkage analysis. The mass spectrum of the carbonyl-reduced and methylated derivative of the monosaccharide **48** from *P. aeruginosa* O7a,7d (Fig. 12) showed the expected fragmentation pattern, which demonstrated the

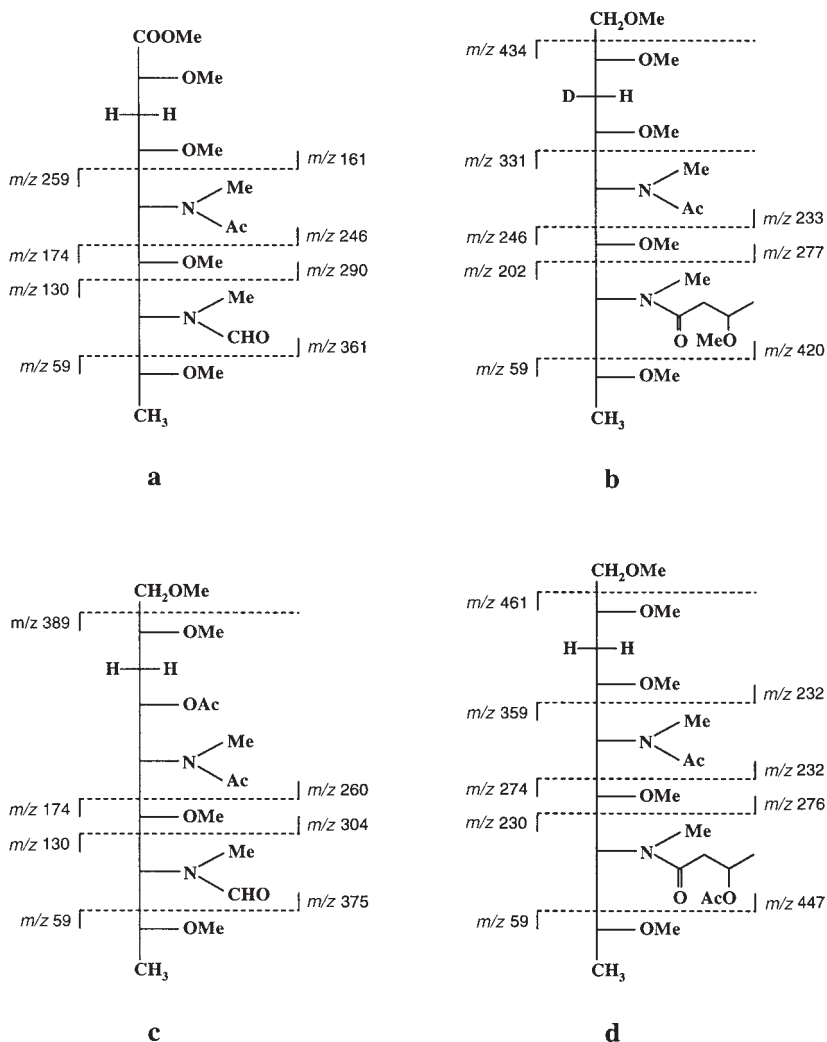


FIG. 17. Electron impact MS fragmentation of the fully (a, b) and partially (c, d) methylated reduced open-chain derivatives of the nonulosonic acids. [Taken from Refs. 9 (d), 14 (b), and 23 (a, c); configuration is not shown.]

position of the amino and deoxy groups and confirmed the identity of the *N*-acyl substituents²³ (Fig. 17a). The pseudaminic acid derivative from CPS of *S. fredii* HH103¹⁴ (Fig. 2) and di-*N*-acetyl-4-epilegionaminic acid from LPS of *L. pneumophila* serogroup 1¹² were carboxyl-reduced before methylation. The mass spectra obtained showed the same general

fragmentation pattern (e.g., see Fig. 17b for the pseudaminic acid derivative).

When the monosaccharide was not available directly after hydrolysis or solvolysis of the polysaccharide, a monomeric derivative for MS analysis could be obtained by a combination of chemical modifications and cleavages. Thus, in order to obtain an open-chain derivative of pseudaminic acid, OPS of *S. boydii* type 7 (Fig. 4, structure 12) was carboxyl-reduced, hydrolyzed under mild acid conditions, the products were carbonyl-reduced, solvolyzed with anhydrous hydrogen fluoride, and methylated.^{9,24}

Linkage analysis was performed on oligosaccharides obtained by a selective cleavage. Thus, carbonyl reduction, carboxyl methylation, and carboxyl reduction of the trisaccharide 46 from OPS of *P. aeruginosa* O7a,7d (Fig. 12) followed by methylation, solvolysis with anhydrous hydrogen fluoride, and acetylation gave a pseudaminic acid derivative that was *O*-acetylated at position 4 and consequently showed the linkage site²³ (Fig. 17c).

Similar methylation analysis demonstrated the glycosidic linkage between a sugar and an *N*-(3-hydroxybutanoyl) substituent of pseudaminic acid in two polysaccharides (Fig. 2). The carboxyl-reduced trisaccharide 45 from OPS of *P. aeruginosa* O9a (Fig. 11) was carbonyl-reduced and methylated.⁹ The open-chain derivative obtained after solvolysis with hydrogen fluoride and acetylation gave the expected electron impact MS fragmentation, which demonstrated *O*-acetylation of 3-hydroxybutanoic acid (Fig. 17d). An alternative sequence was applied to a disaccharide from the CPS 5 of *S. fredii* HH103 (Fig. 2), namely, carbonyl-reduction, methylation, carboxyl-reduction, hydrolysis with dilute trifluoroacetic acid, and a standard conversion to the alditol acetate with *O*-acetyl groups at position 1 of the alditol and position 3 of 3-hydroxybutanoic acid.¹⁴

4. NMR Spectroscopy and Conformational Analysis

a. ¹H NMR Spectroscopy.—The ¹H NMR spectra of reducing 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acid derivatives contained two series of signals belonging to the major and minor anomers with an equatorial and an axial carboxy group, respectively. In each series of the synthetic di-*N*-acetyl derivatives^{11,17,18} (Table III), the signal for the CH₃ group (H-9) was at δ 1.05–1.28 (3H, d, $J_{8,9}$ 6.1–6.6 Hz), two signals for the CH₂ group (H-3) were in the region δ 1.5–2.7, and the resonance region for H-4–H-8 was δ 3.4–4.6.

Both ¹H NMR chemical shifts and the *J*-splitting showed a significant dependence on the relative configuration of the nonulosonic acids. The ³*J*_{H,H} coupling constants for the protons within the pyranose ring (H-3–H-6)

were similar to those observed in hexopyranoses.⁶⁶ The $J_{6,7}$ coupling constant depended on the configuration at C-5: it was small (1.3–3.3 Hz) when NH-5 was equatorial, and large (10.1–10.7 Hz) when axial (Table III). These values were indicative of the *syn*- and *trans*-like relationship for H-6 and H-7, respectively.

The chemical shifts were influenced also by the anomeric configuration. In the nonulosonic acids with an equatorial OH-4, the difference between the ^1H NMR resonances for H-3_{ax} and H-3_{eq} was 0.86–1.02 ppm for the anomer with an axial carboxy group but only 0.21–0.46 ppm for the other anomer, independently of whether NH-5 was axial or equatorial. When OH-4 was axial and NH-5 equatorial, a typical difference of 0.71–0.75 or 0.05 ppm was observed for the anomers with an axial or an equatorial carboxyl group, respectively. In the glycosidically linked nonulosonic acids, the differences were not the same but in most examples were useful for determination of the anomeric configuration of naturally occurring isomers in OPSs and LPSs.^{14,22,23,25,30,31,34–36,40}

The nature of *N*-acyl substituents at N-5 and N-7 and the presence of an *O*-acetyl group at O-4 or O-8 influenced ^1H NMR chemical shifts of the nearby protons. These features could be determined by characteristic chemical shifts and, for *N*-(hydroxybutanoyl) groups, by the corresponding spin systems. The most significant displacement (downfield by 0.9–1.3 ppm) was observed for the signal of the proton at the acetoxylated carbon compared to that at the corresponding hydroxylated carbon. Therefore, comparison of the spectra of the initial and chemically de-*O*-acetylated compounds was used for determination of the *O*-acetylation sites in the nonulosonic acids.^{12,22,39,40}

b. ^{13}C NMR Spectroscopy.—The ^{13}C NMR spectra of each anomer of synthetic 5,7-diacetamido-3,5,7,9-tetradeoxynon-2-ulosonic acids (Table IV) showed nine signals from the sugar moiety, including those of the anomeric carbon C-2 (δ 96.1–97.3), carboxyl group C-1 (δ 174.2–175.9), CH_3 (C-9, δ 16.6–20.4), and CH_2 (C-3, δ 33.3–41.4) groups, three CHOH groups (C-4, C-6, and C-8, δ 66.1–77.3), and two CHNH groups (C-5 and C-7, δ 48.5–55.8), as well as signals for two *N*-acetyl groups (CH_3 at δ 22.9.0–23.5 and CO at δ 174.2–175.9).^{11,17,18}

In sugars with different chirality at C-4 or C-5, predictable chemical shift differences were observed for carbons involved in the pyranose ring (compare data for hexopyranoses⁶⁷). Although epimeric differences at C-7 and C-8 cause less predictable changes in the ^{13}C NMR chemical shifts, some particular regularities could be tracked for the *D*-galacto and *D*-talo isomers, which enabled revision of the configurations of legionaminic and 4-epilegionaminic acids.¹¹ For instance, in sugars with the *D* configuration

at C-8, the C-6 and C-8 signals appeared upfield by 2.0–2.3 and 1.4–2.0 ppm, respectively, compared to the corresponding L epimer. In the *glycero-L-manno* isomers, a significant difference was observed for the C-9 signal, which appeared at δ 20.0 in the D epimer at C-8 but at δ 16.7 in the L epimer (Table IV). This finding was useful for determination of the configuration of pseudaminic acid.

The anomeric configuration had a significant influence on the C-3 and C-6 resonances. Compared to the other anomer, in the anomer with an equatorial carboxy group both signals appeared upfield by 0.8–1.3 and 1.6–2.9 ppm when OH-4 was equatorial or by 2.3–2.6 and 3.8–4.7 ppm, respectively, when OH-4 was axial. The regularity for the C-6 chemical shift was applied for analysis of the anomeric configurations of the naturally occurring nonulosonic acids.^{22,23,35,37,40} Another approach could be measuring $J_{C-1,H-3ax}$ and $J_{C-2,H-3ax}$ long-range coupling constants²⁶ using regularities found for *N*-acetylneuraminic acid.

If an *N*-acetimidoyl group was present instead of an *N*-acetyl group, the ^{13}C NMR signal of the corresponding nitrogen-bearing carbon appeared downfield by 2.9–5.9 ppm (α effect).^{25,31,40} In contrast, compared to an *N*-acetyl group, an *N*-formyl group caused a small upfield α effect of 1–1.5 ppm.²³ Since the *N*-formyl group occurs as two stereoisomers (major *Z* and minor *E*), the ^{13}C NMR spectrum, as well as the ^1H NMR spectrum, showed two sets of signals for the group itself and for the neighboring sugar atoms.²⁷ An influence similar to that of an acetyl group on the ^{13}C NMR chemical shifts was found for 3- and 4-hydroxybutanoyl groups,^{14,20,22,36,37} except for a 3-hydroxybutanoyl group at N-5 of pseudaminic acid, which caused a downfield β effect on C-4 of ~ 1 ppm²³ (Table V).

In accordance with published data on *O*-acetylated hexopyranoses,⁶⁹ an α effect of *O*-acetylation at O-4 or O-8 on the ^{13}C NMR chemical shift was positive (2.3–3.2 ppm), whereas β effects of a similar magnitude on the neighboring carbons were negative^{22,24,31,40} (Table V).

In addition to *N*-acylation and *O*-acetylation, the mode of glycosylation was yet another feature to be taken in consideration for naturally occurring derivatives: whether the sugar was glycosidically linked or had a free anomeric center and whether it was glycosylated itself or occupied a terminal nonreducing position. Comparison of the ^{13}C NMR chemical shifts of the polysaccharides and isolated oligo- and monosaccharides (Table V) as well as the synthetic di-*N*-acetyl derivatives (Table IV) showed that in glycosides C-2 resonated downfield by 2–7 ppm compared to the corresponding free nonulosonic acids. In pseudaminic acid, the effect was larger when the carboxyl group was axial (4–6 vs. 2–3 ppm) (Table V).

TABLE V
¹³C NMR Data of Derivatives of 5,7-Diamino-3,5,7,9-tetradeoxyon-2-ulosonic Acids from Natural Glycopolymers^a

Derivative	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Bacterial Source ¹⁹	Reference
Pseudaminic acid (Pse)										
α-Pse5Ac7(3Hb)	97.7	36.0	66.6	50.1	71.3	54.2	68.4	16.8	<i>Sinorhizobium fredii</i>	14
α-Pse5Ac7Fo	97.6	35.8	66.4	49.9	71.1	52.7	67.6	16.3	<i>Pseudomonas aeruginosa</i> O7a,7d	23
α-Pse5Ac7Fo-(2 →	99.8	36.8	66.3	49.9	72.2	53.9	68.3	17.6	<i>Pseudomonas aeruginosa</i> O7a,7d	23
α-Pse5Ac7(3Hb)-(2 →	99.7	37.2	66.4	49.8	73.1	55.1	69.2	18.3	<i>Sinorhizobium fredii</i>	14
β-Pse5Ac7Ac-(2 →		36.8	67.9	49.6	74.7	54.9	69.5	17.4	<i>Proteus vulgaris</i> O39	28
β-Pse5Ac7(R3Hb)-(2 →	102.1	36.8	67.6	49.0	74.8	54.7	69.2	17.7	<i>Pseudomonas aeruginosa</i> O9a	22
β-Pse4Ac5Ac7(R3Hb)-(2 →	103.0	34.2	70.3	46.4	74.3	54.5	69.4	17.7	<i>Pseudomonas aeruginosa</i> O9a,9b	22
→ 4)-α-Pse5Ac7Fo ^b	97.1	34.8	72.3	46.6	71.2	52.3	67.5	16.3	<i>Pseudomonas aeruginosa</i> O7a,7b,7d	23
→ 4)-α-Pse5(R3Hb)7Fo ^b	96.3	34.8	73.2	46.7	71.2	52.3	67.5	16.3	<i>Pseudomonas aeruginosa</i> O7a,7b,7c	23
→ 4)-α-Pse5Ac7(ZFo)-(2 →	97.6	35.3	72.9	47.1	71.7	52.8	68.2	16.9	<i>Pseudoalteromonas distincta</i>	27
→ 4)-α-Pse5Ac7(EFo)-(2 → ^b	97.6	35.3	72.9	47.0	70.8	54.2	66.7	16.9	<i>Pseudoalteromonas distincta</i>	27
→ 4)-α-Pse5Ac7Fo-(2 → ^b	99.7	35.3	72.2	46.5	71.8	53.5	68.2	17.5	<i>Pseudomonas aeruginosa</i> O7a,7b,7d	23
→ 4)-α-Pse5(R3Hb)7Fo-(2 → ^b	99.6	35.6	73.4	46.6	71.8	53.5	68.3	17.7	<i>Pseudomonas aeruginosa</i> O7a,7b,7c	23
→ 4)-β-Pse5Ac7Ac-(2 → ^b	102.7	36.0	73.5	45.9	75.0	54.5	69.5	17.6	<i>Escherichia coli</i> O136	26
→ 8)-β-Pse5Ac7Ac-(2 → ^c		36.2	67.9	49.3	73.4	53.8	75.0	14.0	<i>Proteus vulgaris</i> O39	28
→ 8)-β-Pse5Ac7(R3Hb)-(2 → ^c	101.5	36.8	67.5	49.7	73.4	54.0	74.4	14.4	<i>Shigella boydii</i> type 7	24
→ 8)-β-Pse4Ac5Ac7(R3Hb)-(2 → ^c	102.5	34.2	70.7	47.1	74.5	54.0	74.5	14.3	<i>Shigella boydii</i> type 7	24
Legionaminic acid (Leg)										
β-Leg5Ac7Ac	97.7	40.9	67.9	54.1	70.8	54.5	68.3	20.4	<i>Vibrio alginolyticus</i>	33
→ 4)-β-Leg5R7Ac ^{c,d}	96.6	36.9	72.7	51.3	70.5	54.0	67.3	20.1	<i>Acinetobacter baumannii</i> O24	35
→ 4)-β-Leg5R7Ac-(2 → ^{c,d}	100.2	37.5	72.7	51.1	70.6	54.0		20.3	<i>Acinetobacter baumannii</i> O24	35
→ 4)-α-Leg5Am7Ac-(2 → ^e	~101	37.6	74.4	54.5	71.1	55.0	67.4	19.1	<i>Vibrio salmonicida</i>	34

→ 4)-α-Leg-(2 → ^c	101.4	38.7	72.3	52.3	71.7	55.8	67.5	19.5	<i>Legionella pneumophila</i> serogroup 1	68
→ 4)-α-Leg5Ac7Ac-(2 → ^e	101.5	40.0	71.6	51.3	73.5	55.1	68.2	20.0	<i>Legionella pneumophila</i> serogroup 1	31
→ 4)-α-Leg5Am7Ac-(2 → ^e	101.8	39.2	71.6	54.2	72.4	55.2	67.7	19.4	<i>Legionella pneumophila</i> serogroup 1	31
→ 4)-α-Leg5Am7Ac8Ac-(2 → ^e	101.6	40.6	71.4	55.1	72.4	52.6	70.8	17.3	<i>Legionella pneumophila</i> serogroup 1	31
<hr/>										
8-Epilegionaminic acid (8eLeg)										
α-8eLeg5Ac7Ac-(2 →	104.0	41.8	69.3	53.8	74.8	54.4	70.1	19.7	<i>Pseudomonas aeruginosa</i> O12	30
α-8eLeg5Ac7Am8Ac-(2 →	99.2	42.6	67.3	53.5	73.6	57.7	73.2	17.3	<i>Shewanella putrefaciens</i>	39
→ 8)-β-8eLeg5(R3Hb)7Ac ^c	96.6	40.7	68.1	53.8	71.6	54.0	73.0	15.6	<i>Salmonella arizonae</i> O61	37
→ 8)-β-8eLeg5(4Hb)7Ac ^c	97.2	40.6	68.2	53.5	70.8	53.8	72.0	14.6	<i>Yersinia ruckeri</i> O1	36
→ 4)-α-8eLeg5Ac7Ac-(2 → ^b	99.7	42.6	78.3	52.2	75.8	55.6	70.0	20.1	<i>Shewanella putrefaciens</i>	39
→ 4)-α-8eLeg5Ac7Am8Ac-(2 → ^b	99.6	42.5	77.0	51.8	74.1	57.8	73.3	17.3	<i>Shewanella putrefaciens</i>	39
→ 8)-α-8eLeg5Am7Ac-(2 → ^b	99.2	42.5	68.5	57.4	74.0	55.2	79.4	19.4	<i>Morganella morganii</i>	38
→ 8)-α-8eLeg5Ac7Ac-(2 → ^c	104.6	42.3	69.5	53.8	73.5	54.5	73.5	15.0	<i>Pseudomonas aeruginosa</i> O12	30
→ 8)-α-8eLeg5(R3Hb)7Ac-(2 → ^c	104.7	42.5	69.2	53.6	73.5	54.4	73.5	15.3	<i>Salmonella arizonae</i> O61	37
→ 8)-α-8eLeg5(4Hb)7Ac-(2 → ^c		42.8	69.8	54.0	74.0	55.4	74.0	16.0	<i>Yersinia ruckeri</i> O1	36
<hr/>										
4-Epilegionaminic acid (4eLeg)										
α-4eLeg5Ac7Ac8Ac		39.7	67.5	49.8	69.5	52.2	70.4	17.1	<i>Legionella pneumophila</i> serogroup 1	12
β-4eLeg5Ac7Ac8Ac	96.5	37.9	67.4	49.6	66.4	52.3	71.5	17.1	<i>Legionella pneumophila</i> serogroup 1	12
→ 4)-α-4eLeg5Am7Ac-(2 → ^e	102.0	40.4	70.3	52.6	69.9	55.8	68.4	19.5	<i>Legionella pneumophila</i> serogroup 2	40
→ 4)-α-4eLeg5Am7Ac8Ac-(2 → ^e	101.9	40.5	69.8	52.7	69.8	52.8	70.7	17.4	<i>Legionella pneumophila</i> serogroup 2	40

^aAll sugars are in the pyranose form. For abbreviations for the *N*-acyl substituents, see note to Table I. Data of the sugar carboxyl group (C-1) and acyl substituents are not shown.

^bSubstituted with a β-D-aldopyranose.

^cSubstituted with an α-D-aldopyranose.

^dR is acetyl or (S)-3-hydroxybutanoyl.

^eSubstituted with an ald-2-ulosonic acid.

In agreement with the general observation of small α -glycosylation effects in ketosides, an α -(2 \rightarrow 4)-ketosidic linkage between two legionaminic acid residues caused a relatively small positive α effect of 2.4 ppm on C-4 and small negative β effects of \sim 1 ppm on C-3 and C-5.³¹ In 4-epilegionaminic acid, the effects were markedly larger (+3.4 ppm on C-4 and -2.9 ppm on C-5²⁷) showing a dependence on the orientation of OH-4.

Glycosylation effects of aldopyranoses demonstrated a clear dependence on the anomeric configuration of the glycosylating sugar. For instance, glycosylation of legionaminic acid at position 4 by an α -D-aldopyranose residue caused a relatively small α effect on C-4 (+4.8 ppm), a relatively large negative β effect on C-3 (-3.8 ppm), and a small positive β effect on C-5 (+1.2 ppm).³⁴ Glycosylation of 8-epilegionaminic acid at the same position by a β -D-aldopyranose residue resulted in significantly different shifts: +9.7 ppm for C-4, +1.4 ppm for C-3, and -1.7 ppm for C-5.³⁹ In pseudaminic acid substituted at position 4 by a β -D-aldopyranose residue, a large negative β effect on C-5 and a smaller β effect on C-3 could be predicted,⁷⁰ and the experimental values were approximately -3 and -1 ppm, respectively.^{23,26}

An α effect on C-8 resulting from glycosylation of pseudaminic acid at position 8 by an α -D-aldopyranose residue was in the range 3.6-5.5 ppm. A negative β effect on C-9 was relatively large in magnitude (3.4-4.2 ppm) and that on C-7 was also negative and small (\sim 1 ppm).^{24,28} Glycosylation of 8-epilegionaminic acid at the same position caused similar glycosylation effects when the glycosylating sugar was an α -D-aldopyranose (α effect of 3.4-5.0 ppm on C-8, β effects of -4.7 to -4.8 ppm on C-9, and 0 to -0.4 ppm on C-7^{22,37}) but different effects when it was substituted by a β -D-aldopyranose (+9.3, -0.3, and +1.3 ppm for C-8, C-9, and C-7, respectively³⁸). An appreciable γ effect (-1.3 to -1.6 ppm) was observed on C-6 of both pseudaminic and 8-epilegionaminic acids independent of the configuration of the glycosyl group.

The dependence of the ^{13}C NMR glycosylation effects, especially β effects, on the anomeric configuration of a glycosylating aldopyranose implies their dependence also on the relative absolute configuration of the glycone and aglycone.^{70,71} As a result, the regularities in the effects of glycosylation of the nonulosonic acids at both pyranose ring (O-4) and the side chain (O-8), together with the effects on C-1 of the glycosylating aldose,^{70,71} enabled determination of the absolute configurations at C-6 and C-8, respectively, provided that the general configuration was established. This approach was used for the determination of the absolute configurations of pseudaminic,²³ legionaminic,³⁴ and 8-epilegionaminic²² acids.

c. NOE Spectroscopy and Molecular Modeling.—Yet another useful tool for the analysis, including determination of the position of the *N*-acyl groups and the configuration of the nonulosonic acids, is nuclear Overhauser effect (NOE) spectroscopy. The location of an acetimidoyl group at N-5 of legionaminic acid in the oligosaccharide **22** from LPS of *V. salmonicida* (Fig. 6) was proved by correlation in a NOESY spectrum between signals for NH-5 and H-5 of the sugar and between NH-5 and the acetimidoyl methyl group.³⁴ A NOESY experiment in combination with a ¹H,¹³C heteronuclear multiple bond correlation (HMBC) experiment enabled determination of the structure and stereochemistry of *N*-methylated acetamidino groups at position 5 of legionaminic acid (**19** and **20**) in OPS of *L. pneumophila*⁴⁴ (Fig. 5).

An example of a stereochemical assignment using a NOESY experiment was the determination of the axial orientation of H-6 by an NOE correlation between H-4 and H-6, which could hardly be done from the *J*_{5,6} coupling constant in the nonulosonic acids with an equatorial H-5, as in pseudaminic acid.²⁶ NOEs observed on preirradiation of protons linked to nitrogen (NH-5 and NH-7) were helpful for the determination of the side-chain configuration and conformation. Thus, the *erythro* configuration of the C-6–C-7 fragment of pseudaminic acid was established by NOEs between NH-5 and H-7 and between NH-7 and H-5 in combination with a relatively large *J*_{6,7} coupling constant (~10 Hz) showing the *trans* relationship between H-6 and H-7 (see earlier). NOE spectroscopy in combination with molecular mechanics calculations was used to confirm the *threo* configuration of the C-6–C-7 fragment of legionaminic acid in LPS of *V. salmonicida*, that is to distinguish between the *glycero*-D-*galacto* and *glycero*-L-*altro* configuration.³⁴ An observation of an NOE between NH-5 and H-7 and no NOE between NH-5 and NH-7 was in accord with the calculated distances in the former but not in the latter. The experiments could be performed either in an H₂O–D₂O mixture²⁶ or applied to a fully *O*-acetylated methyl ester in an organic solvent²⁰ since *O*-acetylation does not significantly change the conformation of the molecules.¹⁸

Conformational studies of methyl (5,7-diacetamido-2,4,8-tri-*O*-acetyl-3,5,7,9-tetradexynon-2-ulopyranos)onates having equatorial OH-4 and NH-5 and different configurations in the side chain showed a *syn* relationship for H-6–H-7 in all four isomers¹⁸ (Fig. 18). This followed from small ³*J*_{H-6,H-7} coupling constant values (1–2.5 Hz) and a strong H-6,H-7 correlation in the NOESY spectra. An HMBC experiment revealed a strong H-6,C-8 correlation in the D-*glycero*-L-*altro* and L-*glycero*-L-*altro* isomers (Fig. 18a and b), thus showing a relatively large ³*J*_{H-6,C-8} coupling constant value and, correspondingly, the *trans* orientation of H-6 and C-8 around the C-6–C-7 bond in the predominant rotamer.

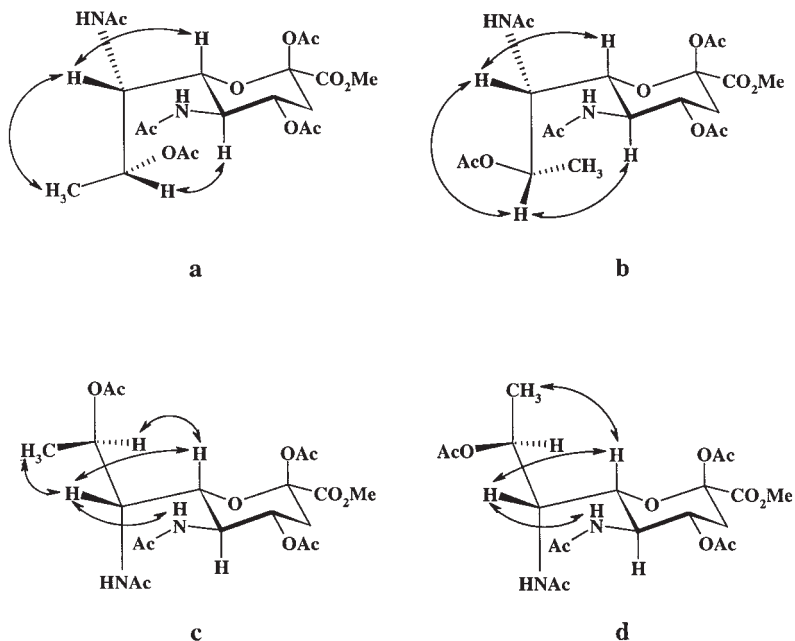


FIG. 18. Selected NOE correlations and conformation of the side chain in methyl (5,7-diacetamido-2,4,8-tri-*O*-acetyl-3,5,7,9-tetradexynon-2-ulopyranos)onates having the *D*-glycero-*L*-*altro* (a), *L*-glycero-*L*-*altro* (b), *D*-glycero-*D*-*galacto* (c), and *L*-glycero-*D*-*galacto* (d) configuration¹⁸

The predominant side-chain conformers were different for the four isomers studied (Fig. 18). The most populated rotamer around the C-7–C-8 bond inferred from NOESY data for the *D*-glycero-*L*-*altro* isomer (Fig. 18a) was in agreement with a small $^3J_{\text{H-7,H-8}}$ value of ~ 1 Hz. In contrast, that for the *L*-glycero-*L*-*altro* isomer (Fig. 18b) was inconsistent with a relatively large $^3J_{\text{H-7,H-8}}$ value (5.0 and 6.8 Hz for the α and β anomers, respectively). This contradiction could be accounted for by a significant contribution of a rotamer with a small H-7–C-7–C-8–H-8 dihedral angle. A relatively large $^3J_{\text{H-7,H-8}}$ value (~ 7 Hz) and only a weak H-7,H-8 NOE correlation indicated the *trans* orientation of H-7 and H-8 in the *D*-glycero-*D*-*galacto* and *L*-glycero-*D*-*galacto* isomers (Fig. 18c and d). NOESY data showed a spatial proximity of H-9 and H-7 in the former (Fig. 18c), whereas in the latter H-9 was more close to H-6 than to H-7 (Fig. 18d).

The conformation of CPS from *S. fredii* HH103 (Fig. 2, structure 5) was investigated using NOE spectroscopy and molecular modeling.⁷² The alternating glycosidic and amidic linkages between 3-hydroxybutanoic acid (*R* and *S* isomers) and pseudaminic acid, together with flexibility in the side

chain of pseudaminic acid, should result in a considerable degree of freedom for rotation between the sugar pyranose rings. Coupling constant values observed for the free monosaccharide indicated *trans*- and *syn*-like relationships for H-6–H-7 and H-7–H-8, respectively, resulting in a conformer with an extended sugar side chain and an extended 3-hydroxybutanoic acid. This was true for both the oligosaccharide fragments and the polysaccharide. “Non-trivial” NOEs observed in the polysaccharide between H-4 of 3-hydroxybutanoic acid and H-6 and H-8 of pseudaminic acid and between H-2a,2b of 3-hydroxybutanoic acid and H-6, H-7, and H-9 of pseudaminic acid were in agreement with the *J* data.

Starting from 27 geometries, molecular mechanics calculations and molecular dynamics simulations were made first on the monosaccharide, then on a disaccharide, and finally on a tetrasaccharide and an octasaccharide in order to simulate the conformations of the polysaccharide of *S. fredii* HH103. The calculations included five of the six torsion angles between the pyranose rings and yielded five low-energy minima, which varied only within 3 kJ, that is, they had almost the same energy. In the glycosidic linkage the φ angle was primarily in a staggered conformation (about 60°), whereas the ψ angle values were around –120° showing a nearly eclipsed disposition between the bonds C-2–O-2 and C-3'–H-3'. This minimized the steric interactions between the sugar ring and both the methyl group and the rest of the side chain. The conformation of the octasaccharide was rather stable and the chain adopted a pseudohelical structure. The average distances between protons found from the molecular dynamics simulations explained satisfactorily most, but not all, of the observed NOEs. A model with alternating (*R*)- and (*S*)-3-hydroxybutanoic acid residues, *SRSR*, could explain the small discrepancies.

IV. CONCLUDING REMARKS

Following the discovery of pseudaminic acid in 1984, 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acid isomers have been found in over 20 bacterial species belonging to different families of Gram-negative bacteria, including enteric bacteria, pseudomonas, vibrios, rhizobia, legionellae, and marine bacteria. The nonulosonic acids have been found primarily in the O-chain polysaccharides of the lipopolysaccharides and several capsular polysaccharides. Recent identification of derivatives of pseudaminic acid in glycoproteins indicate that 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acids may be more common in bacteria than previously believed.

The novel sugars appear to be constituents of important bacterial cell-surface glycopolymers that contribute to pathogenesis. They are structurally related to sialic acids, which are essential components of animal

glycoproteins and glycolipids. Moreover, initial data on the biosynthesis of 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acids suggest that it is similar to the sialic acid pathway. The similarity of the bacterial nonulosonic acids to sialic acids may contribute to bacterial virulence by dampening the immune response to invading bacteria.

Recent advances in NMR spectroscopy and mass spectrometry has contributed much to the progress in the chemistry of the nonulosonic acids. Classical chemical approaches, such as various degradation processes and the synthesis of model compounds, were useful in isolation and characterization of 5,7-diamino-3,5,7,9-tetradexynon-2-ulosonic acid isomers, including solving the questions of chirality. It is likely we will witness the discovery of new isomers and new derivatives in the near-future. Establishing the configuration of new isomers and the nature and location of acyl groups will become easier as analytical techniques improve and data grow. In addition, more sophisticated conformational analysis will enable studies of the interactions between glycopolymers that contain the nonulosonic acids and other biomolecules.

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